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Chronic and treatment-resistant depression

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Abstract

Major Depression does not always remit even with appropriate treatment, and unremitting or difficult-to-treat depression is thought to contribute to the large disease burden caused by depression. Difficult-to-treat depression is an overarching term that can be used to describe depression which is chronic, unremitting or treatment-resistant. The concept of difficult-to-treat depression and the terms used to describe it have not been well validated or universally adopted for use in research and clinical practice. Accordingly, the overarching aim of this thesis was to investigate difficult-to-treat depression, including its conceptualisation and its correlates, with a particular focus on chronic and treatment-resistant depression (TRD). Three methodological approaches were employed to examine this complex phenomenon: 1) a systematic review of the literature; 2) analysis of epidemiological data; and 3) analysis of clinical data.

Randomised controlled trials (RCTs) of treatments for resistant depression (N = 147 trials) were systematically reviewed to identify the current conceptualisation of TRD in the medical scientific literature. The most common definition of TRD was the failure of, or non-response to, two antidepressant trials (N = 58 trials; 39.5%). Major heterogeneity in the conceptualisation of TRD was found with varying study design, differing inclusion/exclusion criteria and inconsistent reporting of treatment history.

Data from the *National Survey of Mental Health and Wellbeing 2007* (NSMHWB) were utilised to estimate the prevalence of chronic or persistent depression. Insufficient treatment data were available to allow the estimation of treatment-resistant depression in community-residing Australians. The newly characterised DSM-5 Persistent Depressive Disorder was modelled and found to have a lifetime prevalence of 4.6% (95% CI: 3.9 – 5.3%) and was found to be present in 29.4% (95% CI: 25.6 – 33.3%) of community-residing individuals with a lifetime depressive disorder. Higher rates of psychiatric co-morbidity (OR = 1.42; 95% CI = 1.26–1.61), older current age (OR = 1.04; 95% CI = 1.02–1.05), a younger age of onset (OR = .97; 95% CI = .95–.98) and more frequent episodes of depression (OR = 1.75; 95% CI = 1.07–2.86) were significant correlates of chronic depression. Differences in health service utilisation associated with chronic depression were assessed to determine whether chronic depression treated in the tertiary care sector was likely to represent TRD. Survey respondents with chronic depression who were treated in tertiary care settings had more complex presentations and many of the clinical features previously associated with TRD, including higher levels of medical and psychiatric co-morbidity, greater traumatic load, higher levels of disability, greater symptom severity and greater risk of attempting suicide.

The findings from the NSMHWB suggested that those whose chronic depression is treated in tertiary care settings may be less responsive to treatment, thus indicating likely TRD. In order to assess the degree of TRD in patients seen in tertiary care settings a sample of depressed inpatients (N = 70) was recruited. The majority of these depressed inpatients had a chronic illness trajectory (N = 64; 91.4%) and had a moderate to high level of TRD as determined by the five existing staging models of TRD. Each of the five staging models of TRD was highly correlated with the other four models, suggesting a substantial degree of agreement between models on their ratings of TRD. An omnibus measure of TRD (M = 0; SD = 4.5) was created by combining the five TRD models into one composite index. Using this composite index as the outcome variable, the following covariates were found to be associated with higher levels of TRD: higher prevalence of suicide attempts (β = 1.71, $t(11) = 3.62$, $p < .001$), older current age ($\beta = 14$, $t(11) = 2.92$, $p < .005$), earlier age of onset (β = -.12, $t(11) = -2.58$, $p < .012$), and poorer cognitive functioning (β = -.16, $t(11) = -2.13$, $p < .038$).

The personality profiles of depressed inpatients with TRD were compared to the profiles of externally sourced controls (healthy controls and depression in remission controls) in order to assess whether personality plays a role in resistance to treatment. In comparison to externally sourced controls, inpatients with TRD demonstrated a personality profile on the NEO-FFI characterised by high neuroticism and openness, together with low extraversion, agreeableness and conscientiousness. The addition of personality factors into a regression model explained a relatively small percentage (R^2 = .14) of the variance in TRD scores, indicating that other, unmeasured, factors may underpin the phenomenon.

The conceptual overlap between chronic depression and treatment-resistant depression, as well as the heterogeneity and inconsistency in the conceptual models of TRD, is highlighted throughout the thesis. The inability to form a consensus on how to define TRD and identify the phenomenon in clinical practice appears to be impeding research efforts aimed at developing treatment strategies for this severely affected group. The reconceptualization of depression using a illness staging model in line with other medical fields such as oncology might be a more appropriate way to conceptualise the disorder and may ultimately lead to improved treatment strategies.

Declaration by author

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Publications during candidature

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Contributor	Statement of contribution
Jenifer Murphy (Candidate)	Conception and design (60%) Wrote and edited the paper (70%) Statistical analysis (100%) Interpretation of findings (70%)
Gerard Byrne	Conception and design (40%) Wrote and edited paper (30%) Interpretation of findings (30%)

Contributions by others to the thesis

Gerard Byrne contributed to the conception and design of the research project. He also made significant contributions to the thesis by editing and critically revising drafts of the thesis. The 2007 National Survey of Mental Health and Wellbeing (NSMHW) was designed, executed and released into the public domain by the Australian Bureau of Statistics (ABS). Clinical data on depressed inpatients were collected at New Farm Clinic. The staff at New Farm Clinic contributed to the collection of data by providing administrative approval for the project to be conducted on site and assisting in the recruitment of participants.

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Keywords

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List of Abbreviations

5-HT	Serotonin receptor
5-HTT	Serotonin transporter
A	Agreeableness
AAR	Antidepressant Resistance Rating
ABS	Australian Bureau of Statistics
ACNP	American College of Neuropsychopharmacology
ACT	Acceptance and commitment therapy
AIHW	Australian Institute of Health and Welfare
APA	American Psychiatric Association
ASL	Arterial spin labelling
ATFH	Antidepressant Treatment History Form
BDI-II	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
C	Conscientiousness
CBT	Cognitive behavioural therapy
CD	Chronic depression
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CIDI-A	Composite International Diagnostic Interview, Automated
CGI	Clinical Global Impression Scale
CoQ10	Coenzyme Q10
CRD	Chronic resistant depression
CSQ	Cognitive Style Questionnaire
CURF	Confidentialised Unit Record File
CV	Coefficient of variation
DALYs	Disability adjusted life years
DAS	Dysfunctional Attitudes Scale
DBS	Deep brain stimulation
DD	Dysthymic Disorder
DoHA	Department of Health and Aging
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-I	Diagnostic and Statistical Manual of Mental Disorders, first edition
DSM-II	Diagnostic and Statistical Manual of Mental Disorders, second edition

DSM-III	Diagnostic and Statistical Manual of Mental Disorders, third edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition text revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
E	Extraversion
ECA	Baltimore Epidemiologic Catchment Area
ECT	Electroconvulsive therapy
ERP	Event-related potential
ESM	European Staging Model
ESS-3	European Social Survey
FFM	Five Factor Model
fMRI	functional Magnetic Resonance Imaging
GABA	Gamma-aminobutyric acid
GORD	Gastro-oesophageal reflux disease
GP	General practitioners
HAM-D	Hamilton-Rating Scale for Depression
HATH	Harvard Antidepressant History Form
HCC	Healthcare for Communities
HCL-32	Hypomania Checklist
HFS	Health and Family Services
HPA	Hypothalamic-pituitary-adrenal axis
HVLT	Hopkins Verbal Learning Test
ICD-10	International Classification of Diseases, tenth revision
ICPE	International Consortium in Psychiatric Epidemiology
IDS-C	Inventory of Depressive Symptomatology
IPT	Interpersonal therapy
K-10	Kessler Psychological Distress Scale
MAC	Medical Advisory Committee
MADRS	Montgomery-Asberg Depression Rating Scale
MAO-A	Monoamine oxidase A
MAO-B	Monoamine oxidase B
MAOI	Monoamine Oxidase Inhibitors
MATS	Michigan Adequacy of Treatment Scale
MBCT	Mindfulness-based cognitive therapy
MDD	Major Depressive Disorder

MDE	Major Depression Episode
MDQ	Mood Disorder Questionnaire
MEDLINE	Medical Literature Analysis and Retrieval System
MINI	Mini International Neuropsychiatric Interview
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MGHS	Massachusetts General Hospital Staging Model
MMP1-2	Minnesota Multiphasic Personality Inventory
MRI	Magnetic resonance imaging
MSM	Maudsley Staging Model
N	Neuroticism
NaSSA	Noradrenaline specific serotonergic antidepressant
NCD	Non-chronic depression
NCS-R	National co-morbidity survey replication
NDRI	Norepinephrine-dopamine reuptake inhibitor
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NEO-FFI	NEO Five-Factor Inventory
NEO-PI	NEO Personality Inventory
NERI	Norepinephrine reuptake inhibitor
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NESDA	Netherlands Study of Depression and Anxiety
NICE	National Institute for Health and Clinical Excellence
NIMH	National Institute of Mental Health
NSMHWB	Australian National Survey of Mental Health and Wellbeing
O	Openness
OLS	Ordinary least squares regression
OR	Odds ratio
PET	Positron emission tomography
PPOC	Personality Profiles of Cultures
PRIME-MD	Primary Care Evaluation of Mental Disorders
PTSD	Post-traumatic stress disorder
QIDS-SR	Quick Inventory of Depressive Symptomatology- Self-report
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RCT	Randomised controlled trial
RDC	Research Diagnostic Criteria

RDoC	Research Domain Criteria
ROC	Receiver operating characteristic
RQ	Research Question
sACC	Subgenual anterior cingulate cortex
SAPAS	Standardised Assessment of Personality – Abbreviated Scale
SARI	Serotonin antagonist and reuptake inhibitors
SCID	Structured Clinical Interview for DSM Disorders
SD	Standard deviation
SIGH-SAD	Structured Interview Guide for the Hamilton Rating Scale for Depression – Seasonal Affective Disorder
SPHERE	Somatic and Psychological Health Report
SNRI	Serotonin and noradrenaline reuptake inhibitor
SMMSE	Standardised Mini-Mental State Examination
SSRI	Selective serotonin reuptake inhibitors
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TCA	Tricyclic antidepressant
TCI	Temperament and Character Inventory
TMS	Transcranial magnetic stimulation
TRAD	Treatment-Resistant Affective Disorders
TRAQ	Treatment response to antidepressant questionnaire
TRB	Treatment-Resistant Bipolar
TRD	Treatment Resistant Depression
TRM	Thase and Rush Staging Model
US	United States
US FDA	United States Food and Drug Administration
VIF	Variance Inflation Factor
VNS	Vagus nerve stimulation
WHO	World Health Organisation
WHO-DAS II	World Health Organization Disability Assessment Schedule
WMH	World Mental Health

Chapter One

Introduction

1.1 History of Depression

The earliest reports of depression as an illness state are found in Ancient Greek medical texts. The physician Hippocrates (460-377 BC) described the symptoms of μελαγχολία (melancholia; from Ancient Greek meaning "black bile") an early representation of depression, as the aversion to food, despondency, sleeplessness, irritability and restlessness (Horwitz & Wakefield, 2007). The philosopher Aristotle (384-322 BC) subsequently identified disordered sadness as being disproportionate to life events. He hypothesised that a melancholic temperament may leave individuals vulnerable to developing a melancholic disorder and queried:

> Why is it that all men who have become outstanding in philosophy, statesmanship, poetry or the arts are melancholic and some to such an extent that they are infected by the diseases arising from black bile... they are all, as has been said, naturally of this character.

Aristotle likened the aetiology of depression to the fermentation process of wine and referenced the humoral theory[1] and an excess of black bile as the cause of melancholia (Zimmerman, 1995). Black bile was thought to ferment over time to produce varying levels of depression and anger (Zimmerman, 1995). Humoral theorists related variations in black bile to the cause of an individual's disposition and behaviour as well as explaining the differences in character traits between disturbed and well-adjusted individuals (Radden, 2002). Building on the humoral theory, the physician Galen (AD 131-200) developed one of the first typologies of mental disease and temperament (Jackson, 1978). He proposed four temperamental types: 1) sanguine - full of impulsivity and excitability; 2) melancholic - serious, dour and downcast nature; 3) choleric - emotional sensitivity; and 4) phlegmatic - detachment and impassivity (Matthews, 1999; Flaskerud, 2012). Variations or imbalances in the humors together with a quality of warmth, coldness, dryness and/or moisture lead to one of the four temperaments (Matthews, 1999; Flaskerud, 2012). In the case of a melancholic temperament, an excess of black bile together with the qualities of coldness and dryness resulted in patients who were "fearful, sad, misanthropic and tired of life" (Jackson,

[1] The humoral theory is an early Western medicine principle originating during antiquity. The theory proposes that the human body is comprised of four humors (black bile, yellow bile, phlegm and blood). Good health is considered to be a balance between the four humors with disease denoted by an excess or deficit of one or more humors (Jackson, 1878).

1978). Not only did Galen develop one of the first personality typologies, he was also one of first to recognise melancholy as long-lasting and recurrent (Jackson, 1978).

Christianity's overarching influence during the Middle Ages resulted in supernatural explanations for mental illness (Lewis, 2012). As an example, demonic possession was considered to be the cause of depression and madness, and was treated by the church through exorcism or burning rather than by medieval medicine (Lewis, 2012). Demonology rather than natural or biological causes to mental illness was favoured during the Middle Ages (Matthews, 1999). On reflection it is thought that many accused of witchcraft or demonic possession during the Middle Ages were most likely mentally ill (Matthews, 1999). Johann Weyer (1515-1588) a prominent physician of the time spoke out against the doctrine of demonology and advocated for further consideration of the natural causes of mental disease (Matthews, 1999). Despite the introduction of asylums for the mentally ill during the fifteenth century, doctrines of witchcraft and demonology maintained its prominence during the sixteenth century with increased popularity of astrology, palm reading and fortune telling (Matthews, 1999). It was during this period, when great emphasis was placed on otherworldly beings controlling the events of the world, that the term lunatic was coined, referring the observation of greater disturbance in the mentally ill under the presence of the moon (Matthews, 1999).

The following century was known as "*The Era of Reason and Observation*" with a shift towards more rational and natural explanations for mental illness (Matthews, 1999). Robert Burton, perhaps the most famous Renaissance sufferer of melancholy, wrote a compendious review of melancholia detailing his own personal suffering (Burton, 1621 cited in Knoff, 1975). Often considered to be ahead of his time, Burton postulated that melancholy was rooted in the unconscious mind and was caused by internal conflicts, traumatic loss and heredity (Burton, 1621 cited in Knoff, 1975). Pre-empting Freud by a few hundred years and the rise of psychoanalysis, Burton suggested melancholic sufferers confess their grievances to a "discreet, trusting friend" (Burton, 1621 cited in Knoff, 1975).

While reforming the asylums of the sixteenth and seventeenth centuries, Philipe Pinel (1745-1826) of France recognised the importance of psychosocial factors in the development and maintenance of mental disease (Matthews, 1999). With likeness to the contemporary biopsychosocial model, Pinel listed what he believed to be the causes of mental disease and incorporated inherited factors, other biological factors (e.g. fever, head injury, non-bleeding haemorrhoids), psychological factors (a melancholic constitution), and psychosocial factors (an irregular way of life, harmful social environment) into a single aetiologic model (Matthews, 1999).

The modern era of psychiatry began in the nineteenth and twentieth century with German psychiatrist, Emil Kraepelin (1856-1926). Kraepelin was a pioneer in the field of biological psychiatry, arguing that depression and other mental disorders are brain diseases (Lewis, 2012). He is also considered be the first to introduce diagnostic models of mental disorders and distinguish between mood disorders (e.g. depression) and thought disorders (e.g. psychosis) (Lewis, 2012; Ebert & Bar, 2010). Alternative explanations for mental disorders, such as those deriving from Sigmund Freud's psychoanalysis, gained greater attention in the late 1920s. By the 1960s, psychiatry was divided into multiple schools of thoughts. Public demand for accountability, criticism of institutionalisation, and the widespread use of psychotropic medication saw a shift away from psychoanalysis and back to biological psychiatry pioneered by Emil Kraepelin and Adolf Meyer (1866-1950) (Sabshin, 1990).

1.2 Modern Conceptualisation of Depression

Kraepelin is most notably known as the forefather of nosology in psychiatry and the person most often associated with the disappearance of the term *melancholia* and the emergence of its replacement *depression* (Shorter, 2013). Kraepelin's psychiatric nosology titled *Compendium der Psychiatrie* was first published in 1883 (Kraepelin, 1883). In later editions of his psychiatric compendium he proposed two distinct mental illnesses which he termed dementia praecox (later referred to as Schizophrenia) and manic-depressive disorder (later referred to as Bipolar Disorder) (Kraepelin, 1893 cited in van Praag, 2008). He determined that mental illness could be separated into two distinct disorders which could be distinguished by unique symptomatology and illness course (van Praag, 2008). His nosology of mental disease was developed based on his independent collection of longitudinal data on 899 patients in Munich during the late nineteenth century (Fox, 2002). Kraepelin broadly categorised manic-depressive illness with an acute onset and remission within a period of months (Healy, 2013). He also observed the chronic and recurrent nature of manic-depressive illness reporting that recurrent episodes were common with the duration of episodes increasing over time (Fox, 2002). The depression component of manic-depressive illness was reported to last 6 to 8 months but longer episodes lasting 2 to 4 years were not uncommon (Fox, 2002).

Unlike contemporary affective disorder nosology, Kraepelin's definition of manic-depressive disorder was an all-inclusive category for any pathological changes in mood (Zivanovic & Nedic, 2012). Included in his classification of manic-depressive disorder were single and recurrent episodes of the disorder, episodes of depression only (unipolar depression), episodes of mania, psychotic and more severe forms of the disorder as well as mild cases of the disorder and

pathological personality characteristics (Zivanovic & Nedic, 2012). He suggested a common underlying psychopathology and aetiology to all of the above states and hinted toward a spectrum of mood disorders (Zivanovic & Nedic, 2012). In line with Aristotle and other historical figures in psychiatry, Kraepelin proposed manic-depressive insanity was disproportional to life stressors and was not directly caused by external stressors (Paykel, 2008). This theory was in direct contrast to the other emerging school of thought of the time, psychoanalysis (Paykel, 2008). Psychoanalysts, such as Freud, developed their own aetiological theories linking depressive states to actual or symbolic object loss (Paykel, 2008). The mediator of these two competing theories was Adolf Meyer who considered the importance of both psychological stress and biological factors in the aetiology of depressive states (Paykel, 2008).

Meyer was an outspoken critic of Kraepelin's nosology, and placed greater emphasis than Kraepelin had on life history and individual differences between patients rather than on symptom clusters and disease entities (Grob, 1991). Despite the opposition of Meyer and others to the "*one person, one disease*" nosology, a *Statistical Manual for the Use of Institutions for the Insane* (1918) was developed in response to an increased push for and expansion of epidemiological data collection. The first nine editions of this *Statistical Manual* were influenced by biological aetiological theories of mental illness and included only one non-psychotic disorder (Grob, 1991). The tenth edition of the manual included psychoneuroses and gave greater attention to somatic and non-psychotic disorders (including reactive depression), which were thought to have psychological rather than biological causes (Grob, 1991).

World War II cemented the conceptual shift toward psychological rather than biological aetiological theories of mental illness (Grob, 1991). American military physicians witnessed first-hand the effects of trauma and psychological distress on and off the battlefield (Grob, 1991). These physicians utilised supportive forms of psychotherapy to treat psychoneuroses that developed in response to trauma (Decker, 2007; Grob, 1991). Wartime physicians reported 60% of traumatised soldiers treated with supportive psychotherapy returned to the battlefield with 2 to 5 days (Grob, 1991). The success of treating psychoneuroses during World War II renewed interest in psychodynamic and psychoanalytic treatments for the general population (Decker, 2007; Grob, 1991). Many of the military physicians returning from World War II moved into the field of psychiatry and were critical of the previous *Statistical Manual* based on Kraepelin's nosology. The main criticism was that the *Statistical Manual* was not applicable to the general population who required help, "dealing with the problems of ordinary life" (Grob, 1991). Post-war psychiatrists were identifying mild personality disturbances and the presence of psychosomatic disorders in the general population which were not categorised appropriately in the then current *Statistical Manual*

(Grob, 1991). They related the causes of these disorders to psychodynamic theory and considered such factors as complex parent-child relationships, the impact of loss, emotional maturity and role adjustments (Grob, 1991).

In response to growing criticism of the *Statistical Manual for the Use of Institutions for the Insane*, the first edition of the *Diagnostic and Statistical Manual of Mental Disorders, First Edition, (DSM-I*) was published in 1952 by the American Psychiatric Association (APA). The manual originated from psychiatric nosology devised by American military psychiatrists during and after World War II (Grob, 1991). The DSM-I (American Psychiatric Association, 1952) was heavily influenced by prominent psychodynamic theories of the late 19th and mid 20th centuries and classified *Depressive Reactions* as:

> …precipitated by a current situation, frequently by some loss sustained by the patient, as is often associated with a feeling of guilt for past failures or deeds. The degree of the reaction in such cases is dependent upon the intensity of the patient's ambivalent feeling toward his loss (love, possession) as well as upon the realistic circumstances of the loss. (p.33-34)

Alternatively, depression characterised by a "gross distortion or falsification of external reality (delusions, hallucinations, illusions)" was classified as a psychotic disorder in the DSM-I (American Psychiatric Association, 1952). The dichotomy of neurotic or reactive depression versus psychotic or endogenous depression is one of the major controversies surrounding the development of the DSM and its subsequent editions (Paykel, 2008). In the United Kingdom, the subdivision of depression into endogenous/psychotic and reactive/neurotic was strongly debated. Prominent Welsh psychiatrist Robert Kendell outlined the main pitfalls of classifying depression in the *British Journal of Psychiatry* in 1976. He noted the difficulties validating depression without any biological or pathophysiological markers and commented on the controversy surrounding the subdivision of depression into endogenous/psychotic and reactive/neurotic depression (Kendell, 1976). Kendell summarised the typologies and models (e.g. Paykel, Eysenck) of the time and advocated for the separation of endogenous/psychotic and reactive/neurotic depression (Kendell, 1976). He favoured a dimensional approach to the subdivision of depression citing evidence from factor analysis studies, that failed to consistently find more than one discrete type of depression (Kendell, 1976). Despite evidence supporting a dimensional approach, the classification of depression as either endogenous/psychotic or reactive/neurotic was maintained in second edition of the DSM published in 1968 as it was still highly influenced by psychodynamic theories.

The development of the DSM-III (1980) led to an atheoretical approach to classification, defining disorders based on symptom clustering and clinical attributes rather than theory. This approach has been maintained in the most recent edition of the DSM published in 2013 (American Psychiatric Association, 2013). The DSM-III has its foundation in the diagnostic criteria developed by psychiatrists at the Washington University namely, John Feighner, Eli Robins, Samuel Guze and George Winokur (Decker, 2007; Feighner et al., 1972; Horwitz & Wakefield, 2007). Feighner and colleagues developed fourteen diagnostic criteria for psychiatric illnesses and one criterion for secondary depression based on empirical data and systematic reviews of previous medical scientific literature (Decker, 2007; Feighner et al., 1972). The move toward data-driven diagnostic classifications for psychiatric illnesses was reminiscent of Kraepelin, with Feighner, Robins, Guze and Winokur named the "neo-Kraepelinians" (Decker, 2007; Horwitz & Wakefield, 2007). The Feighner Criteria were published in the *Archives of General Psychiatry* in 1972 and this became the most highly cited psychiatric paper of the time (Decker, 2007). The return of Kraepelinian and Meyerian type thinking and the introduction of the Feighner Criteria gave rise to the Research Diagnostic Criteria (RDC; Spitzer, Endicott and Robins, 1978) which shaped the third edition of the DSM with a greater emphasis on scientific research and reliability of classification (Decker, 2007). Despite echoing Kraepelin and attempting to improve diagnostic reliability, the RDC and editions of the DSM failed to consider causes of mental illness as Kraepelin had, thus remaining atheoretical even to aetiology (Decker, 2007).

The RDC introduced the term, *Major Depression*, as the overarching label for clinical depression still used today. The term was coined as a label for "an episode of serious depressive illness" and was considered "general enough to encompass the many further subdivisions" of the illness (Spitzer, Endicott & Robins, 1978 pg.777). The RDC introduced anhedonia as an alternative criterion to dysphoric mood for diagnosing depression (Spitzer, Endicott & Robins, 1978). The endorsement of either a dysphoric mood or anhedonia to meet criteria for Major Depression was integrated into the DSM-III and subsequent editions. According to the authors of the RDC, the rationale for providing anhedonia as an alternative criterion is based on clinical presentations of depression which show patients do not always acknowledge their depressed mood (Spitzer, Endicott & Robins, 1978). The RDC is also responsible for denoting a required symptom duration, another major trait of the disorder still maintained today. The required symptom duration to meet criteria for diagnosis was reduced from one month (as specified in the Feighner criteria) to two weeks in RDC and DSM editions without a clear rationale (Spitzer, Endicott & Robins, 1978).

The DSM-III closely followed the RDC but was most notable for distinguishing unipolar depressive disorders from bipolar disorders. The third edition of the DSM rejected the previous

nosological classification of proportionate reactions to loss and only excluded individuals from a diagnosis of depression who were recently bereaved (American Psychiatric Association, 1980). The bereavement exclusion was maintained in the DSM-IV (1994) and the DSM-IV, text revision (TR) (2000) but has been removed from the DSM-5 published in 2013.

The DSM-IV and DSM-5 diagnosis of Major Depression evolved from DSM-III criteria and still required symptoms to be present for a two week period to meet diagnostic criteria. The DSM-IV-TR and DSM-5 symptoms of depression are characterised into three categories: 1) emotional symptoms; 2) cognitive symptoms; and 3) vegetative symptoms. The DSM-5 diagnosis of Major Depressive Disorder (MDD) requires the presence of at least one Major Depressive Episode (MDE) (see Table 1.1). In this thesis the term depression refers to the diagnosis of Major Depression either MDE (single episode) or MDD (two or more episodes). When further clarification is required the exact diagnosis will be provided.

Although the DSM-IV and DSM-5 is the preferred clinical diagnostic system for health professionals in the United States of America and Australia, the International Classification of Diseases, tenth revision (ICD-10) is used as the official coding system for disease in Australia, Europe and other countries (Andrews, Slade, & Peters, 1999). The ICD-10 requires the presence of two (of three) key symptoms of depression (feeling sad, losing interest or lacking energy) to meet diagnostic criteria whereas, the DSM-IV and DSM-5 requires either a depressed mood or loss of interest or pleasure to meet diagnostic criteria (see Table 1.1). The DSM-IV and ICD-10 diagnoses of depression have high concordance, leading many to suggest that their diagnostic criteria should be harmonised (Andrews, Slade, & Peters, 1999).

Table 1.1

DSM-5 Major Depressive Disorder (MDD) criteria (single episode or recurrent)

Major Depressive Disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
    1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad, empty, hopeless) or observation made by others (e.g. appears tearful)
    2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or by observation)
    3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
    4. Insomnia or hypersomnia nearly every day
    5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
    6. Fatigue or loss of energy nearly every day
    7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
    8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
    9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan or a suicide attempt or specific plan for committing suicide

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

1.3 Subtypes of Depression

First introduced in the DSM-III, Affective Disorders is the broad category that includes Major Depression and various other mood disorders and their subtypes. The DSM-III also set the precedent to separate unipolar and bipolar depression in the DSM-IV-TR and DSM-5. The division between unipolar and bipolar depression is in direct contrast to Kraepelin's all-inclusive view of affective disorders where mania, hypomania, depression, mixed states and depressive temperaments were all considered to share the same aetiology and vary along a spectrum of mood disorders (Benazzi, 2006).

The categorical approach to mood disorders is one of the main criticisms and areas of controversy surrounding contemporary diagnostic classification systems of mood disorders. Not only are bipolar and unipolar depression considered separate entities in the DSM-IV-TR and DSM-5 both disorders can also be classified by illness course and subtype according to symptomology and presentation. For the purpose of this thesis only unipolar depression subtypes will be discussed.

Using the DSM-5, depression (single episode or recurrent) can be categorised in terms of severity (mild, moderate, severe and psychotic) and can be specified by course (in-partial remission, in full remission and unspecified). Additional specifications such as catatonia, melancholia, atypical features, anxious distress, mixed features, mood-congruent psychotic features, mood-incongruent psychotic features, peripartum onset and seasonal pattern exist for Major Depression criteria in the DSM-5. Adding specifiers to the diagnosis of depression in the DSM describes the differences in clinical presentations but does not specify or comment on aetiology and whether different types of depression have differing or shared aetiologies. The lack of comment on aetiology is an inherent issue across all disorders not just subtypes outlined in the DSM.

In addition to specifying distinct features of the depressive episode there are also several subtypes of depression that can be classified. Subtypes of depression were identified based on symptom diversity and heterogeneous presentations of depressed patients in clinical practice (van Loo et al., 2012). The major diversity in presentation, symptomatology, treatment response and aetiology suggests that for some purposes, homogeneous subtypes may be more appropriate classification systems than the overarching classification of Major Depression (van Loo et al., 2012). Identifying subtypes of depression may also aid treatment selection and improve treatment response (Benazzi, 2006). Attempts to validate the depressive subtypes and prove their clinical utility has been difficult due to inconsistent findings and reliance on pre-established and atheoretical categorical nosology (Gili, et al., 2012). The two subtypes of depression which have received the most attention in regards to treatment response and the heterogeneity of depression, are atypical and

melancholic subtypes (Gili, et al., 2012). The differences in symptomatology between the two subtypes are reflective of the historical distinction between reactive and endogenous depression.

The predominant differentiating feature of atypical and melancholic depression is mood reactivity. Atypical depression is defined by the presence of mood reactivity, as well as the presence of at least one of the following features: increased appetite, hypersomnia, leaden paralysis and the personality trait of interpersonal rejection sensitivity (Benazzi, 2006). In contrast, melancholic depression is characterised by lack of mood reactivity, as well as by loss of pleasure, early morning awakening, depression worse in the morning, marked psychomotor retardation or agitation, significantly decreased appetite, and excessive guilt (Benazzi, 2006).

The majority of atypical depression research reviewed by Stewart et al. (2007) categorised it as having an early age of onset and a more chronic illness trajectory. In comparison, melancholic depression is thought to have a later age of onset and to be a non-chronic illness (Stewart et al., 2007). There are also familial and genetic aetiological factors that are likely to be associated with depression subtypes. For example, Kendler et al. (1996) studied 1000 female twin pairs and found that when both twins reported a depressive episode, it was more likely that either both or neither twin had atypical depression than just one twin.

In older medical scientific literature atypical and melancholic depression were thought to have different treatment response trajectories. Atypical depression was thought to respond better to monoamine oxidase inhibitors (MAOIs) compared to tricyclic antidepressants (TCAs) (Liebowitz et al., 1988; Stewart et al., 2007), whereas TCAs were reported to be more effective than selective serotonin reuptake inhibitors (SSRIs) in treating melancholic depression (Perry, 1996). However, these findings have not been supported by subsequent systematic reviews or recent studies investigating differences in treatment response among the various subtypes of depression (melancholic, anxious and atypical) (Uher et al., 2011). The general consensus is that melancholic subtype represents a more severe form of depression but it is not associated with poorer response to SSRIs or other antidepressant classes once baseline demographics and clinical variables are accounted for (Hadzi-Pavlovic & Boyce, 2012; McGrath et al., 2008).

The validity of depression subtypes and their utility in clinical practice has been debated (Kessing, 2007). So far the evidence is inconclusive to suggest a clear differentiation in clinical presentation and long-term outcomes between patients with distinct depression subtypes (Kessing, 2007). The criticisms and controversies surrounding depression subtypes are synonymous with contemporary conceptualisations of depression, most notably the categorical nature of current diagnostic classification systems (Kessing, 2007).

1.4 Validity of Current Diagnostic Classification Systems

Current nosologies define mood disorders as discrete entities using a categorical framework in an attempt to differentiate normality from pathology (Sunderland et al., 2013). Major Depression was introduced in the DSM-III with the primary purpose of delineating normal sadness due to bereavement from sadness without cause (Horwitz & Wakefield, 2007). However, with the recent removal of the bereavement exclusion from the DSM-5 criteria for Major Depression there is a concern that current classification systems have lost the ability to make this distinction and as a consequence are medicalising grief and normal sadness (Eyers, 2013). Even prior to the removal of the bereavement exclusion, the validity of the DSM's conceptualisation of depression was questioned (Horwitz & Wakefield, 2007; Parker, 2007).

Firstly, the criteria used to identify Major Depression largely ignore the heterogeneous clinical presentation of depression and require the endorsement of depressed mood or anhedonia together with an arbitrary number of other symptoms to meet diagnostic criteria (Parker, 2005). This results in major variability in symptomatology and heterogeneous clinical presentations. As a consequence, the natural history, illness course and treatment response are difficult to estimate on the individual and population level. In addition, aetiology and factors related to response are related to the individual rather than the disorder (Parker, 2005). As Parker (2005) points out, the DSM's atheoretical classification of Major Depression was designed purposefully not to provide any "meaningful information about aetiology, prognosis and treatment" of depression. This approach has led to lower than expected efficacy rates of treatments for depression and the lack of standardised treatment approaches (Parker, 2005).

The trial-and-error approach to treatment is supported by the Treatment Guidelines published by the RANZCP which propose four different antidepressant classes and two forms of psychotherapy as treatments for moderate to severe depression which clinicians can employ at their own discretion (Parker, 2005). This has resulted in clinicians treating patients according to their own "treatment paradigms" rather than treating the patient according to the features of the disorder (Parker, 2005). Additionally, clinicians select antidepressants based on subjective judgements of efficacy and tolerability, as evidence to support one antidepressant over another is inconclusive (Nierenberg, 2010). Assessing the efficacy of treatments for depression was the rationale behind the STAR*D study (see section *1.10.1 STAR*D*), the largest study of treatments for depression to date (Nierenberg, 2010). However, despite enrolling over 4000 depressed outpatients the study failed to develop an evidence-based treatment paradigm indicating which patients will respond to which antidepressant (Nierenberg, 2010).

The introduction of antidepressants as viable treatments for depression created the illusion that depression was easily treatable with reports that endogenous/melancholic depression was more responsive to antidepressant therapy compared to reactive/atypical depression (Parker, 2000). In more recent times, researchers and clinicians have shifted their view from depression as a treatable, acute illness to a chronic and recurrent illness that does not always respond to treatment (Katon, Unutzer & Russo, 2010). The evidence suggesting endogenous/melancholic depression was more responsive to physical treatments strengthened the support for categorical classification systems and the demarcation of bipolar versus unipolar depression. The heterogeneous clinical presentation of depression and the high rates of psychiatric co-morbidity are also considered to be a failure of the categorical classification systems (Regier et al., 2009). Individuals with depression can have a mix of co-morbidities from multiple disorder groups including mood, anxiety and personality disorder groups (Regier et al., 2009). Evidence of poorer response to treatment in depression with co-morbid anxiety disorders together with the high prevalence of co-morbid anxiety disorders with depression, provides further evidence that categorical classification systems fail to capture the heterogeneity in clinical presentations (Boyce, 2013).

The current categorical classification systems largely ignore differences in severity, treatment response, illness course and aetiology (Kessing 2007). Spectrum/dimensional classification systems identify depression along a continuum based on severity of symptoms and vary from depressed personality features to chronic and more severe forms of depression. For an individual, depression can change across the illness course and over their lifetime. Thus individuals can move along the depression spectrum over time (Kessing, 2007). A spectrum/dimensional classification system also considers and incorporates subsyndromal conditions due to poor response to treatment or never receiving treatment (Sunderland et al., 2013). Although a spectrum/dimensional conceptualisation of depression may be more appropriate in some situations, it has critics. According to Sunderland et al. (2013), this approach is too complex and has limited clinical utility. The primary purpose of employing discrete diagnostic entities is to improve communication not only between researchers and clinicians but also between patients, policy makers and insurance companies. Employing a spectrum approach to diagnosis may limit communication between these parties and impede future research efforts (Sunderland et al., 2013).

The main issue surrounding all classification systems is how to simplify complex heterogeneous presentations in a meaningful way. Presently, classifications systems are trying to do too much in order to meet the needs of all relevant parties (e.g. patients, doctors, researchers and insurance companies). On one hand, they are trying to identify patients using narrowly defined criteria for research purposes while at the same time trying to provide a broad classification system

to facilitate communication among patients, doctors, government agencies and insurance companies. Attempting to meet these divergent needs has resulted in an unsatisfactory classification system for all parties.

The DSM-5 provided an opportunity to re-conceptualise the classification of psychiatric disorders (Boyce, 2013). However, aside from the removal of the bereavement exclusion, no other significant changes were made to the Major Depression criteria. The National Institute of Mental Health (NIMH) is developing a biologically valid framework for identifying psychiatric disorders using behavioural, genetic and neurobiological markers. This classification system has been labelled the Research Domain Criteria (RDoC) and is in direct response to the DSM's lack of validity, its atheoretical approach to aetiology and the reliance on symptom clusters rather than objective biological markers to diagnose disorders (Insel et al., 2010). This project is still under development and is not yet a replacement for the DSM-5 or ICD-10. At this point in time, the DSM-5 and ICD-10 categorical diagnostic systems are the best available resources to researchers and clinicians to identify and treat mental illness. However, despite being the "best available", the DSM-5 and ICD-10 classification systems do not reflect our current level of knowledge on the aetiology of mental illness.

1.5 Epidemiology of Depression

1.5.1 Prevalence. The prevalence of depression has been difficult to consistently estimate due to variations in research methodology, recall bias, sampling and diagnostic criteria (Kessler & Bromet, 2013). Despite these difficulties, cross-national and population comparisons of the prevalence of depression using valid and structured measures provide estimates of disease burden. These estimates highlight the differences in cultural presentations of depression and reflect the magnitude of the problem for healthcare providers and governments.

The World Health Organisation (WHO) actioned the World Mental Health (WMH) survey using the WHO Composite International Diagnostic Interview (CIDI) to obtain worldwide prevalence estimates and correlates of mental, substance and behavioural disorders (Kessler & Bromet, 2013). The WMH-CIDI is a fully structured diagnostic interview used to assess psychiatric disorders and treatment utilisation in the community (Kessler & Ustun, 2004). Households were sampled using multistage household probability sampling (Kessler & Bromet, 2013). Eighteen countries participated and were divided into high income and low-to middle-income countries. High-income countries included the United States, France, New Zealand, Belgium, Germany, Israel, Italy, Japan, Netherlands and Spain. Low-to-middle-income countries included Brazil,

Colombia, India, Lebanon, Mexico, China, South Africa and Ukraine. The lifetime and 12-month prevalence of DSM-IV MDE in high-income counties was reported to be 14.6% and 5.5%, respectively (Kessler & Bromet, 2013). Compared to high-income countries, the lifetime prevalence of DSM-IV MDE was lower in low-to-middle-income countries at 11.1%. However, the 12-month prevalence of DSM-IV MDE in low-to-middle-income countries was comparable to high-income countries, 5.9% and 5.5% respectively.

In the Australian context, community based studies of the prevalence of depression have revealed similar rates of depression as the WMH surveys. The Australian National Survey of Mental Health and Wellbeing (NSMHWB) was conducted in 1997 and 2007 to assess the prevalence of common psychiatric disorders and health service utilisation of Australian community residing individuals. In 1997, 10600 community residing individuals over the age of 18 were interviewed using the Composite International Diagnostic Interview, Automated (CIDI-A) (Henderson, Andrews, & Hall, 2000). The 12-month prevalence of a depressive disorder (ICD-10 depressive episode or Dysthymia) was 5.8% (Hendersen, Andrews, & Hall, 2000). In the 2007 survey, one person between the age of 16 and 85 from 8841 households was interviewed using select modules from the WMH-CIDI. The lifetime prevalence of an affective disorder was 15% and the 12-month prevalence of DSM-IV MDE was 4.1% (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). Over a ten-period between the two national surveys (1997 to 2007) the 12-month prevalence of affective disorders rose from 5.8% (Hendersen, Andrews, & Hall, 2000) to 6.2% (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). Additionally, the prevalence of Major Depression in the state of South Australia, as assessed by the Mood module of the Primary Care Evaluation of Mental Disorders (PRIME-MD), increased from 6.8% in 1998 (N = 3010) to 10.3% in 2008 (N = 3034) (Goldney, Eckert, Hawthorne, & Taylor, 2010).

Community-based studies in the United States (Compton, Conway, Stinson, & Grant, 2006; Kessler, et al., 2007) and Europe (Hagnell, Ojesjo, Otterbeck, & Rorsman, 1994; Andrade, et al., 2003) also report an increase in the prevalence of depression over time and in subsequent generations (Hidaka, 2012). The effects of modern life including obesity, poor diet, sleep deprivation and social competition have been suggested to contribute to the increasing prevalence of depression (Hidaka, 2012). Alternatively, the estimated rise of depression may be inflated. Between study periods and over time there have been variations in the conceptualisation of depression, sampling methods, response bias and/or attrition, resulting in misleading prevalence estimates when epidemiological studies are compared side by side (Hawthorne, Goldney, & Taylor, 2008). Whether or not the prevalence of depression is increasing over time, it is currently highly prevalent in both high and low-to-middle income countries (Kessler & Bromet, 2013). By 2030

depression is expected to be the highest contributor to the global disease burden (World Health Organization, 2008).

1.5.2 Illness course. Major Depression occurs across the lifespan and is commonly reported in late adolescence, early to middle adulthood and in late adulthood (Kessler & Bromet, 2013). The mean retrospective age of onset reported across all WMH surveys was in early adulthood (20-29 years old) with the peak risk period for the onset of MDE ranging from mid to late adolescence (15-22 years old) to mid adulthood (40-49 years old) (Kessler & Bromet, 2013). Three longitudinal population based studies (See Table 1.2) provide much needed information on the course of depression. These studies, one from the United States and two from the Netherlands, use longitudinal research methods to estimate the duration of a depression episode, time to recovery from a depression episode and rate of chronicity in community-residing individuals. The studies estimate the median duration of depression episodes to be between three and six months (Spijker, de Graaf, Bijl, Beekman, Ormel, & Nolen, 2002; Penninx, et al., 2011; Eaton, Shao, Nestadt, Lee, Bienvenu, & Zandi, 2008). Time to recovery, defined as no or minimal symptoms of depression in the preceding three months (Spijker, de Graaf, Bijl, Beekman, Ormel, & Nolen, 2002; Penninx, et al., 2011) or a full year without an episode of depression (Eaton, Shao, Nestadt, Lee, Bienvenu, & Zandi, 2008) is likely to occur between six months and three years post onset of episode.

The Baltimore Epidemiologic Catchment Area (ECA) study (see Table 1.2) reported that approximately 50% of depressed participants with a first-lifetime episode of depression recover and do not experience any future episodes of depression. Over the 23-year follow-up period the remaining participants in the ECA study experienced either an unremitting chronic course (approximately 15%) or initially recovered and subsequently experienced future episodes of depression (approximately 35% of participants) (Eaton, Shao, Nestadt, Lee, Bienvenu, & Zandi, 2008). A chronic illness trajectory, defined as a symptom duration greater than two years, was reported in 20 to 24.5% of participants in other longitudinal community-based studies (see Table 1.2). In addition, in wave one (N = 43093) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) conducted in the United States the estimated prevalence of chronic depression in individuals with a lifetime diagnosis of MDD was 24.0% (Rubio et al., 2011). Thus, evidence from longitudinal community-based studies suggests that the course of depression can be chronic and unremitting in a substantial minority of individuals with depression.

1.5.3 Sociodemographic correlates. Cross-national community epidemiological studies highlight an association of gender, age and marital status with depression (Kessler & Bromet, 2013). Depression is more prevalent in females than males independent of sampling method, diagnostic system and location (Kessler, Mcgonagle, Swartz, Blazer, & Nelson, 1993). Results from

the WMH surveys and the European Social Survey (ESS-3), which surveyed 18 and 23 countries respectively, report that females are twice as likely to be depressed than males (Van de Velde, Bracke, & Levecque, 2010; Bromet, et al., 2011). Additionally, in the year 2000, the Global Burden of Disease study reported a higher disease burden of depression in females compared to males: 5.6% vs. 3.4% of total disability adjusted life years (DALYs) (Ustun, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). The gender gap in depression is likely multifactorial in origin and may involve genetics, biological factors such as hormonal changes and greater hypothalamic-pituitary-adrenal axis (HPA) disturbance, and psychosocial factors, including gender role stressors and cultural influences (Kuehner, 2003).

In developed countries, the WMH surveys found recent MDE are more prevalent in younger respondents than in those aged 65 years old and older (Kessler, et al., 2010b). The International Consortium in Psychiatric Epidemiology (ICPE) surveys conducted between 1990 and 1999 in 10 counties (Canada, United States, Brazil, Chile, Mexico, Czech Republic, Germany, Netherlands, Turkey and Japan) reported younger cohorts as having a higher prevalence of MDE (Andrade, et al., 2003). However, in younger cohorts, episodes were less persistent (as indicated by the ratio of 12-month to lifetime prevalence) than older cohorts (Andrade, et al., 2003). This indicates younger cohorts may present with a higher number of new cases of depression whereas, older cohorts are more likely to have a persistent and chronic course of depression. An alternative explanation is that an increase in the proportion of new cases of depression in younger cohorts is "accompanied by a decrease in the persistence of these new cases of depression" (Andrade, et al., 2003).

Across all 10 countries in the ICPE surveys, individuals who had never been married had a higher prevalence of MDE than married individuals (Andrade, et al., 2003). In high-income countries there were strong associations between MDE and being separated and never married whereas in low-to-middle income countries there were strong associations between MDE and being divorced and widowed (Kessler & Bromet, 2013). Findings from the ESS-3 show lower levels of depression in married individuals or individuals in civil relationships than in divorced, separated, widowed or never married individuals (Van de Velde, Bracke, & Levecque, 2010). Overall, in community-residing individuals, depression is more prevalent in females, younger cohorts and in individuals who are not married.

Table 1.2

Longitudinal population-based studies assessing the course of depression

Study	Origin	Study design (year; N)	Follow-up period (years)	Diagnostic criteria	Median episode duration (months)[e]	Time to recovery[e]	Chronicity (percentage of participants) [e]
NEMESIS[a]	Netherlands	Three waves: T_0 (1996; N = 7076), T_1 (1997; N = 5618), T_2 (1999; N = 4796)	2	DSM-III-R MDE using the WMH-CIDI, version 1.1 and Life Chart Interview	3	8.4 months (mean)	20% not recovered after 2 years
ECA[b]	United States	Three waves: T_0 (1981; N = 3481), T_1 (1993; N = 1920), T_2 (2004; N = 1071)	23	Diagnostic Interview Schedule and Life Chart Interview	3	2 or 3 years (median)	15% not recovered after 23 years
NESDA[c]	Netherlands	Two waves: T_0 (2004; N = 2981), T_1 (2006; N = 2596)	2	DSM-IV MDD using WMH-CIDI, version 2.1 and Life Chart Interview	6	6 months (median)	24.5% not recovered after 2 years
NESARC[d]	United States	Two waves: T_0 (2001-2002; N = 43093), T_1 (2004-2005; N = 34653)	2	DSM-IV MDD using the Alcohol Use Disorder and Associated Disabilities Interview Schedule	N/A	N/A	N/A

[a]Spijker, de Graaf, Bijl, Beekman, Ormel, & Nolen, 2002; [b]Eaton, Shao, Nestadt, Lee, Bienvenu, & Zandi, 2008; [c]Penninx, et al., 2011; [d]Rubio et al., 2011 and Garcia-Toro et al., 2013; NEMESIS, The Netherlands Mental Health Survey and Incidence Study; ECA, The Baltimore Epidemiologic Catchment Area; NESDA, The Netherlands Study of Depression and Anxiety; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions;T_0, baseline, T_1, wave 1;T_2, wave 2; DSM-III-R, Diagnostic and Statistical Manual, third edition revised; WMH-CIDI, World Mental Health Composite International Diagnostic Interview; MDE, Major Depressive Episode; MDD, Major Depressive Disorder; N/A, not available

[e]*Note*. Data was not available for the NESARC

1.6 Models of Depression

In order to explain and understand depression, conceptual frameworks incorporating either single or multifactorial causes have been developed. During different historical periods, particular models of depression have attracted greater interest and attention as a result of conceptual or research advances of the time (Lewis, 2012).

1.6.1 Psychodynamic models. The psychodynamic model is a combination of many psychoanalytic theories which all share a common assumption that early, unresolved, patterns of feelings lead to difficulties adapting and living in the world (Lewis, 2012). Psychodynamic theories of depression evolved from Freud's distinction between mourning and melancholia (Ouimette & Klein, 1993). According to Freud, a bereaved person directs anger inward towards a loved object due to perceived abandonment and this in turn results in depressive symptoms and lowering of self-esteem (Gabbard, 2005, Ouimette & Klein, 1993). Depression is thought to occur in a similar way to bereavement, but the type of loss experienced is expanded to include interpersonal rejection and the loss of ambitions or ideals (Ouimette & Klein, 1993). Individuals who have a history of forming insecure attachments are considered to be more susceptible to developing depression because they are more likely to experience hostility following a loss (Ouimette & Klein, 1993).

Other psychoanalysts such as Abraham (1924), Rado (1928) and Fenichel (1945) have associated depression with regressed behaviours and feelings in line with the oral-sadistic stage of early development (cited in Carducci, 2009). The oral stage occurs during the first 18 to 24 months of life and is the period of time when a child receives pleasure and tension release from eating and placing objects in their mouth (Carducci, 2009). This is also the period when a child is weaned from its mother (Carducci, 2009). How this loss and conflict is reconciled at this early stage is thought to have important implications for personality development and future conflicts (Carducci, 2009). Individuals with depression are reported to have oral-dependent behaviours (e.g. alcoholism, smoking, chewing) and rely on external narcissistic supply (e.g. positive or negative attention) to bolster and maintain self-esteem (Ouimette & Klein, 1993). The lowering of self-esteem, as a feature of depression, in psychodynamic theories is thought to be activated due to narcissistic frustrations including anal (e.g. lack of control), phallic (e.g. achievement related) and oral needs (Ouimette & Klein, 1993). Following on from Freud's theory of object loss, Edith Jacobson (1971) suggested depressed individuals mimic the behaviours of the lost object and become victim to the superego, presenting as helpless and hopeless (Gabbard, 2005). This behaviour is perhaps an attempt to reconcile with the perceived lost object and bring about its return.

Modern psychoanalysts, such as Bowlby (1980) and Blatt (1974), put forward interpersonal/object-relational theories of depression which have their foundations in earlier psychodynamic theories. Bowlby is one of the fathers of Attachment Theory and defined attachment as the "lasting psychological connectedness between human beings" (Bowlby, 1969 pp 194). Attachment styles are developed in early childhood and are thought to influence later interpersonal relationships and personality (Ouimette & Klein, 1993). An anxious or self-reliant attachment style is associated with depression (Ouimette & Klein, 1993). Individuals with an anxious attachment are described as being excessively dependent and fear abandonment from significant others. This attachment style is thought to develop in response to parental neglect and/or the feeling of responsibility in relation to parental abandonment. The second attachment style linked to depression is the self-reliant attachment style which develops in response to parental criticism and rejection of love and affection (Ouimette & Klein, 1993). Similarly, Blatt (1974) proposed two types of depression which evolve from interpersonal concerns relating to care and dependency developed during early childhood (anaclitic) or a preoccupation with self-definition, self-worth and identity resulting in achievement-related concerns (introjective) (Reis & Grenyer, 2002).

All psychodynamic theories share a similar theme, that early childhood experiences and development unconsciously influence a person's personality and interpretation of life events. In relation to depression more specifically, the common factor across all psychodynamic theories is object loss and a person's reaction and attempt to reconcile a particular loss as the root cause of depression symptoms. Psychodynamic therapy attempts to resolve depression by reducing the feelings of grief, anger and disappointment due to the experienced or perceived loss (Lewis, 2012).

1.6.2 Cognitive models. Cognitive models of depression hypothesise that thought processes surrounding the way an individual thinks about their self perception and the world around them, are involved in the onset, maintenance and recurrence of depression over time (Kircanski, Joormann & Gotlib, 2012). The three major cognitive models are Beck's cognitive theory (1976), the hopelessness model (Abramson, Metalsky & Alloy, 1989) and response styles theory (Nolen-Hoeksema, 1991; Possel & Knopf, 2011). All three models share a common theme of "cognitive vulnerability-stress" which attempts to explain why some people develop depression while others do not. To put more simply, cognitive vulnerabilities interact with life stressors, activating negative thought processes (Possel & Knopf, 2011). Cognitive models underpin many contemporary psychological therapies for depression including Cognitive Behavioural Therapy (CBT).

1.6.2.1 Beck's cognitive theory. Cognitive theory pioneer, Aaron Beck proposed biased acquisition and processing of information is involved in the development and maintenance of depression over time (Beck, 1967). Information processing is influenced by activation of schemas

to internal or external events. Schemas are structures "for screening, coding and evaluating stimuli," ideas and experiences that exert great influence over thoughts, attitudes and behaviours (Beck, 1967). Rooted in early life, negative self-referential schemas are activated by adverse events (Beck, 1967). They are subsequently activated by future stressors, which are reflective of early life activation (Beck, 1967; Disner, Beevers, Haigh, & Beck, 2011). When negative self-referential schemas are activated it results in an increased vulnerability for depression by altering information processing, attention, interpretation and memory (Disner, Beevers, Haigh, & Beck, 2011). Biased attention, processing and memory is characterised by three primary cognitive patterns labelled the "cognitive triad": 1) construing experiences in a negative way; 2) viewing the self in a negative way; 3) viewing the future in a negative way (Jackson, 1986). These negative automatic thoughts, together with biases in attention, processing and memory, result in a ruminative response style, perpetuating negative thoughts about the self, the world and the future (Disner, Beevers, Haigh, & Beck, 2011). A feedback loop is initiated which drives the development, maintenance and recurrence of depression (Disner, Beevers, Haigh, & Beck, 2011).

1.6.2.2. Hopelessness model. The hopelessness model of depression was developed by psychologist Lyn Yvonne Abramson (1989) and colleagues, who proposed hopelessness depression as a unique subtype of depression characterised by reduced motivation, lowered locus of control, sad affect, suicidal ideation, reduced energy and psychomotor retardation (Spangler et al., 1993). Their model theorises that an individual's attributional style (defined as characteristic tendencies to explain the cause of events and behaviours) together with negative life events interact to develop hopelessness depression (Spangler et al., 1993). Attributional style is conceptualised as two dimensions (stable-unstable and global-specific). In relation to hopelessness depression, individuals who consider negative events as stable (i.e. long-lasting) and global (i.e. infiltrate many aspects of their life) are more likely to experience hopelessness depression than individuals who do not hold that particular attributional style (Spangler et al., 1993).

Negative life events and difficulties functioning in interpersonal and achievement domains are considered to be the stressors which interact with a depressed attributional style (inferring causes as stable and global) resulting in hopelessness depression (Spangler et al., 1993). For individuals with an interpersonal diathesis, hopelessness depression can be triggered when individuals experience a perceived loss, rejection or interpersonal conflict (Spangler et al., 1993). In comparison, individuals who have an achievement diathesis and who experience a performance failure or goal frustration are more likely to experience hopelessness depression when viewing the causes of their failure or frustration as stable and global (Spangler et al., 1993).

1.6.2.3 Response style theory. In likeness to Beck's cognitive theory and the hopelessness model of depression, response style theory suggests that the way in which an individual responds to a depressed mood determines the development, severity and duration of the depression episode (Possel, 2011). There are vast differences in severity and illness duration between individuals who experience depression. For some individuals, depression is mild and short-lived while for others depression can be severe, impair functioning and reoccur. The response style theory attempts to explain these differences in presentations by identifying the type of response that an individual has to their depressed mood (Just & Alloy, 1997).

According to response style theory there are two primary response styles employed by depressed individuals labelled rumination and distraction (Nolen-Hoekesma, 1991). Rumination is a response style defined as, "behaviours and thoughts that focus one's attention on one's depressive symptoms and on the implications of these symptoms" (Nolen-Hoekesma, 1991 pg. 569). Examples of rumination are; consistent thoughts about why one feels depressed, expressing how one feels to others and continually thinking about the consequences of feeling depressed (Just & Alloy, 1997). The second response style is distraction (Nolen-Hoekesma, 1991). Individuals with a distractive response style initiate activities to ignore the symptoms of depression (e.g. concentrating on work and engaging in pleasurable activities). A ruminative response style is thought to be linked to more severe and enduring depression symptoms than those with a distractive response style (Nolen-Hoekesma, 1991). In comparison to other response styles, rumination is considered to emphasise the negative effects of the depressed mood and reflects the cognitive pattern detailed in Beck's cognitive triad (Sarin, Abela & Auerbach, 2005). Rumination is also considered to affect problem solving as it impairs attention and concentration reducing the likelihood of the individual employing behaviours that could reduce the severity of symptoms (Sarin, Abela & Auerbach, 2005).

1.6.2.4 Integrating cognitive models of depression. When reviewing the main cognitive models of depression the similarities between the models are difficult to ignore. Similarities between the models highlight the opportunity to integrate the models into one primary cognitive model of depression (Possel & Knopf, 2011). One study examined the relationship between the primary cognitive constructs of all three models (depressed schemas, stable and global attributional styles and rumination) and confirmed that the constructs were distinct but highly correlated with one another in a student population (Hankin et al., 2007). A more recent study by Possel and Knopf (2011) investigated whether the three cognitive models could be integrated using a student population in Germany (N = 588). Like Hankin et al. (2007), they found that the primary constructs of all the models were independent but could be integrated based on mediating relationships (Possel & Knopf, 2011). One component of a ruminative response style, brooding (i.e. melancholic

pondering), was found to influence depressive symptoms when mediated by Beck's automatic thoughts (Possel & Knopf, 2011). In addition, Beck's cognitive triad was associated with attributional style only when response style provided a mediating link between depressive symptoms and attributional style (Possel & Knopf, 2011). To date, Possel and Knopf's (2011) integrated model has not been replicated in clinical populations to assess its validity and utility. However, the successful integration of the primary cognitive models stands to improve current psychological therapies of depression by combining empirically validated constructs of depression leading to more appropriately tailored and effective therapeutic techniques.

1.6.3 Psychosocial model. Brown and Harris (1978) proposed a psychosocial model of depression which implicated specific psychosocial factors named "vulnerability factors", together with certain "provoking agents" as the root cause of depression in women. Brown and Harris (1978) developed their theory of depression based on findings from an aetiological study of depression in British women (N = 458). The vulnerability factors identified were: 1) three or more children under the age of 14 at home; 2) lack of an intimate relationship with spouse/partner; 3) unemployment; and 4) loss of a mother before the age of 11 years old (Patten, 1991). Brown and Harris (1978) reported that the presence of vulnerability factors on their own was not associated with an increased risk of depression and that certain provoking agents, defined as severe life stressors and life difficulties, were also required to increase the risk of depression. Over time, Brown and Harris' (1978) model of depression has been tried and tested with the majority of studies failing to replicate the model (Patten, 1991).

In more recent times, certain aspects of Brown and Harris' (1978) model have been replicated and expanded upon. In particular, early adverse events in childhood including the loss of a parent, parental neglect and childhood abuse have been associated with an increased risk of depression and anxiety disorders in adulthood (Brown & Harris, 1993). Using epidemiological data, it has been reported that at least 30% of adulthood psychiatric disorders are related to childhood adversities (cited in McLaughlin et al., 2010). The majority of epidemiological studies investigating the association between psychopathology and early child adversity have focused on first episode onset rather than lifetime persistence of the disorder (McLaughlin et al., 2010). McLaughlin and colleagues (2010) utilised data from the National Co-morbidity Survey Replication (NCS-R) (N = 9282) and assessed the relationship between early childhood adversities and persistence of DSM-IV psychiatric disorders over time. Persistence was calculated using a ratio of current prevalence to lifetime prevalence as determined by data collected during the NCS-R using the World Health Organisation Composite International Diagnostic Interview (CIDI). The persistence of mood disorders was associated with maladaptive family functioning (parental mental illness, family

violence, physical abuse, sexual abuse) but not with any other childhood adversities including parental divorce, medical illness or economic hardship (McLaughlin et al., 2010).

Other psychosocial factors have been found influence the course of depression. The influence of positive and negative life events on the depression illness course has been studied. Negative life events can precipitate an episode of depression and are associated with the recurrence of episodes over time (cited in Spinhoven et al., 2011). Conversely, positive life events have been associated with remission of depression episodes (cited in Spinhoven et al., 2011). A large epidemiological study, The Netherlands Study of Depression and Anxiety (NESDA) which followed 1209 participants with depression and/or anxiety investigated the relationship between life events and the course of depression and/or anxiety over a two year period (Spinhoven et al., 2011). At the two- year follow-up the presence of negative life events (i.e. serious illness, death of close friend/relative, unemployment and financial loss) and positive life events (i.e. met new partner, became friends, new job or promotion and financial benefit) were assessed (Spinhoven et al., 2011). Unsurprisingly, negative life events were predictive of longer time to remission in individuals with depression (Spinhoven et al., 2011). Participants were asked to date the occurrence of these events to determine the temporal relationship between remission and the event occurring. Using this approach, Spinhoven and colleagues (2011) were able to determine that negative life events but not positive life events predicted time to remission. The authors conclude that negative life events are independently associated with the depression illness course and that interventions should aim to minimise the effect of negative life events on the individual and the resulting stress surrounding the event by targeting resilience and coping strategies (Spinhoven et al., 2011).

1.6.4 Evolutionary models. As the models above highlight, adversity and negative life events are strongly associated with depression. Low mood, grief and sadness may be useful in certain circumstances but when it becomes "excessive, prolonged or expressed in the wrong situation" it can be become pathological and detrimental to an individual's fitness (Nesse, 2000). Charles Darwin (1887) recognised that "pain or suffering of any kind, if long continued, causes depression and lessens the power of action; yet it is well adapted to make a creature guard itself against any great or sudden evil" (cited in Nesse, 2000). To evolutionary theorists, depression can be considered an adaption which may function to communicate a need for help, signalling defeat in a hierarchy conflict, enabling disengagement from commitments to unattainable goals and regulating patterns of investment (Nesse, 2000).

Darwin hypothesised that depression and anxiety evolved as reactions to temporary losses (e.g. physical separation from primary care giver) with the aim of re-establishing physical proximity as soon as possible (Hagen, 2011). Bereavement reactions are considered to be a consequence of

this adaption as physical proximity cannot be re-established (Hagen, 2011). Low mood and sadness may have evolved as beneficial responses to adversity, whereas disproportionate sadness or depression without cause is considered a dysfunction of this adaptation (Hagen, 2011). In response to adversity, an individual can trigger internal signals (e.g. influencing one's own behaviour) and external signals (e.g. crying, suicidal behaviours, anhedonia) in order to influence other people and to elicit care and help (Hagen, 2011). One evolutionary theory suggests that disproportionate sadness or depression occurs in response to complex adverse problems which require complex solutions and analysis (Hagen, 2011). Excessive rumination and anhedonia (e.g. reduced interest in surroundings) may function to promote problem solving and analytical reasoning (Hagen, 2011). In addition, external signals (e.g. deliberate self-harm and suicidality) could be an adaptive a form of help seeking. Partners and significant others often provide help in response to depressive symptoms (Hagen, 2011). In relationships which require a significant other to produce benefit (e.g. work, marriage, and parenthood), suicide can be perceived as harmful to both individuals' fitness and therefore works as a strong motivator for the non-depressed individual to help (Hagen, 2011). Suicide attempts and deliberate self-harm are risky ventures for the individual and would only be a valid solution for individuals whose work, marriage, health and/or parenthood were failing (Hagen, 2011). In return, suicide would be costly for individuals if work, marriage, health and/or parenthood were going well. These "successful" individuals could not afford to express external signals of suicide and depression as it may negatively impact their current and future benefits (Hagen, 2011).

Another evolutionary theory highlights recent evidence that depression is often accompanied by inflammatory or immune related responses (Anders, Tanaka, & Kinney, 2013). Symptoms of depression may have adaptive utility in protecting against infection and may be activated by the immune status of the individual (Anders, Tanaka, & Kinney, 2013). Considering depression has an hereditary component, evolutionary theory suggests symptoms which activate a variety of behavioural and physical responses, may be adaptive by helping individuals and their kin fight current and avoid future infections (Anders, Tanaka, & Kinney, 2013).

1.6.5 Biological models. Current and historical reports of depression as an illness state highlight the physical symptoms accompanying the depressed mood (i.e. insomnia, psychomotor retardation, fatigue and appetitive changes) resulting in ongoing interest and research into the biological aetiology of depression. Investigations between depressed and non-depressed samples have found differences in neurotransmitter function, hormones, brain structure and immune function suggesting multiple biological factors, independently or together, may predispose, precipitate or be caused by depression (Garcia-Toro & Aguirre, 2007). Following the introduction of antidepressants, biological theories of depression based on antidepressant class and mechanism

of action have been proposed (see Table 1.3). In more recent times, the attention has shifted toward genetic differences and the interaction between stress, the environment and genetic vulnerabilities in the manifestation of depression.

1.6.5.1 Neurotransmitter and antidepressant models of depression. The introduction of Monoamine Oxidase Inhibitors (MAOIs) as treatments for depression led to the development of the monoamine theory of depression. In the 1950s, MAOIs were first developed as treatments for tuberculosis and were found to improve mood in patients being treated. The monoamine theory relates depression to decreased activity of monoamine neurotransmitters such as norepinephrine (noradrenaline), dopamine and serotonin (Mulinari, 2012). Monoamine Oxidase Inhibitors work by inhibiting the action of the enzyme monoamine oxidase, which has two isoforms, MAO-A and MAO-B. Inhibition of monoamine oxidase prevents the breakdown of several monoamines including epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine and serotonin, thus increasing the availability of these neurotransmitters at the synapse. In the following decade, tricyclic antidepressants (TCAs) were introduced as viable treatments for depression. Like MAOIs, TCAs also have multiple mechanisms of action and work on multiple monoamine transmitters. Their main therapeutic modes of action in depression are serotonin and norepinephrine (noradrenaline) reuptake inhibition. The balance between serotonin and norepinephrine inhibition differs depending on the type of TCA (Yildiz, Gonul & Tamam, 2002). For example, clomipramine has higher inhibitory action at the serotonin reuptake pump whereas desipramine has higher inhibitory action at the norepinephrine reuptake pump (Yildiz, Gonul & Tamam, 2002).

Unlike MAOIs and TCAs, most of the newer generation of antidepressants do not have a broad mechanism of action. Drugs in one of the newer antidepressant classes, the selective serotonin reuptake inhibitors (SSRIs), effectively only inhibit the reuptake of serotonin. They are considered to be safer than TCAs and MAOIs, which act upon multiple monoamine transmitters and have more serious adverse effects. SSRIs are now commonly used as first-line antidepressants in primary care settings. Serotonin and norepinephrine reuptake inhibitors (SNRIs) inhibit the reuptake of norepinephrine as well as serotonin, but behave more like SSRIs than MAOIs or TCAs. Other newer classes of antidepressants such as norepinephrine reuptake inhibitors (NERIs), noradrenergic and specific serotonergic antidepressants (NaSSA), norepinephrine-dopamine reuptake inhibitor (NDRI) and dopaminergic reuptake inhibitors also act on monoamines and have reinforced the importance of the monoamine system in depression (Goldstein et al., 2011). Table 1.3 provides a summary of each antidepressant class and their main mechanism of action.

Table 1.3

Summary of antidepressant classes and their main mechanism of action

Line of treatment	Antidepressant class (Example)	Main mechanism of action
1st line	SSRI (Fluoxetine)	Selective 5-HT reuptake inhibitor
	NERI (Reboxetine)	Reuptake inhibitor for norepinephrine and epinephrine
	NaSSA (Mirtazapine)	Noradrenergic and specific serotonergic antidepressants
	NDRI (Bupropion)	Blocks the action of the norepinephrine transporter
2nd line	SNRI (Venlafaxine)	Blocks reuptake of norepinephrine and serotonin
	TCA (Clomipramine)	Blocks reuptake of multiple monoamines
3rd line	MAOI (Phenelzine)	Irreversibly inhibits the mitochondrial enzymes Monoamine oxidase A (5-HT) and B (noradrenaline and epinephrine)

Note. Adapted from Malhi, Hitching, Berk, Boyce, Porter, and Fritz, 2013
SSRI, selective serotonin reuptake inhibitor; NARI, noradrenaline reuptake inhibitor, NaSSA, noradrenaline and specific serotonergic antidepressant; NDRI, norepinephrine-dopamine reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor; SARI, serotonin antagonist and reuptake inhibitors; 5-HT, serotonin receptor

Aside from decreased monoamine activity related to antidepressant action, depression has also been linked to reduced gamma-aminobutyric acid (GABA) activity (Hasler, 2010). Dysregulation of the glutamate system and deficits in GABAergic activity are implicated in depression due to their involvement in the stress response, hippocampal neurogenesis, dysregulation of brain-derived neurotrophic factor (BDNF) and decreased serotonin and norepinephrine gene expression (Sharpley, 2013; Luscher, Shen, & Sahir, 2011).

The role that neurotransmitters play in depression is not yet fully understood. Although antidepressants increase the concentrations of neurotransmitters at the synapse within hours or days of treatment, an improvement in mood may not been seen for weeks or months, if at all (Sharpley,

2013). Therefore it is likely that neurotransmitters contribute to the pathophysiology of depression in a complicated interaction with other biological (e.g. HPA axis), genetic (e.g. serotonin transporter gene) and environmental (e.g. stress) factors.

1.6.5.2 Genetic. Family, twin and adoption studies support evidence that depression is a familial disorder with genetic factors explaining approximately 30 to 40% of the variance in the development of the disorder (Sullivan, Neale, & Kendler, 2000; Hasler, 2010). Genetics may influence the development of depression in multiple ways (Sharpley, 2013). Particular genes may interact with environmental factors (e.g. stress or adversity) leading to an increased or decreased vulnerability to depression (Sharpley, 2013). Additionally, specific genes or a particular expression of genes may predispose an individual to depression (Sharpley, 2013). The majority of genetic research has focused on the serotonin transporter gene, which has emerged as a target of research due to its association with SSRIs (Goldstein et al., 2011). Individuals who carry a short (s) allele of the serotonin transporter gene (S-carriers) are thought to have impaired transporter function and are more likely to experience depression after stressful life events or early adversity (Goldstein et al., 2011). Continued or long-lasting transporter dysfunction may alter the sensitivity of serotonin receptors resulting in an increased vulnerability to stress and depression (Goldstein et al., 2011). Despite the association between impaired serotonin transporter and increased vulnerability to stress the presence or absence of the S-allele has not been shown to predict response to SSRIs (Goldstein et al., 2011).

Other targets of research are the genes related to neuroprotective or neurotrophic processes (Tamatam, Khanum & Bawa, 2012). These processes have been implicated in the survival, function, growth and development of neurons in the brain. Brain-derived neurotropic factor (BDNF) is a nerve growth factor which is considered to have antidepressant-like effects and may be associated with the aetiology of mood related phenotypes (Tamatam, Khanum & Bawa, 2012). BDNF is involved in neurotrophic processes, helping to maintain the health of brain neurons. When an individual is under stress, the BDNF gene is repressed which damages the neurons in the hippocampus and is thought to lead to depression (Tamatam, Khanum & Bawa, 2012). Animal models and BDNF mechanistic hypotheses propose that recurring depression may result in continued atrophy of the neurons in the hippocampus and subsequently poorer response to treatment (Tamatam, Khanum & Bawa, 2012). Genetic variations in BDNF have not been found to predict treatment response or remission in individuals with depression (Tamatam, Khanum & Bawa, 2012). However, lower levels of BDNF have been found in individuals with depression supporting the theory that depression and treatment response may be related to the atrophy of neurons in the hippocampus in response to stress (Tamatam, Khanum & Bawa, 2012).

1.6.5.3 Structural. Prior to the introduction of antidepressants, physicians discovered that they could stimulate exposed areas of the brain to evoke mood and emotional phenomenon (Feldman & Goodrich, 2001). They also reported that destroying the same brain regions using surgical techniques resulted in changes to mood and behaviour (Feldman & Goodrich, 2001). These early findings concentrated subsequent research on the orbitofrontal cortex, frontal lobe, basal ganglia and temporal lobe in relation to depression. The most prominent findings from functional and structural magnetic resonance imaging (MRI) and post-mortem studies are abnormalities in the left subgenual cingulate cortex in depression (Hasler, 2010). It has been suggested that the subgenual cingulate is involved in emotional processing with dysfunction in this particular area implicated in the pathogenesis of mood disorders (Greicius, et al., 2007). Other structures in the limbic system (e.g. the hypothalamus, amygdala and hippocampus) have also been associated with depression (Drevets, 2000; Roy & Campbell, 2013).

Alterations of the hypothalamic-pituitary-adrenal (HPA) axis, a system of feedback associations between the hypothalamus, pituitary gland and adrenal glands, are considered to reduce hippocampal volume and prefrontal cortex activity in depression (Palazidou, 2012). Reduced hippocampal volume has consistently been linked to depression and is thought be a consequence of recurrent episodes of depression (Videbech & Ravnkilde, 2004). The importance of the hippocampus in understanding the pathophysiology of depression is also supported by the presence of the monoaminergic and glutamatergic systems in the hippocampus, which are networks of neurons involved in antidepressant action and response (see *1.6.5.1 Neurotransmitter and antidepressant models of depression*) (Roy & Campbell, 2013). It is not clear whether structural alterations in depression are a state effect, which are reversible, or if they predate the onset of depression and worsen over time (Palazidou, 2012). However, there is clear evidence to support the association of hyperactivity in the HPA axis with an increase in the stress hormone, cortisol, and depression (Sharpley, 2013).

1.6.5.4 Stress. Stress is a response to a stimulus (stressor) which precipitates a reaction in the brain activating physiologic systems in the body (stress response) (Tamatam, Khanum & Bawa, 2012). The physiologic response to stress results in the release of neurotransmitters and hormones sending messages to the rest of body eliciting stress responses (Tamatam, Khanum & Bawa, 2012). Stress can be short-lived or long-lasting. Chronic stress, which is long-standing, can have negative effects on the body and has been linked to the aetiology of many diseases (Tamatam, Khanum & Bawa, 2012). Stress can also reduce the efficacy of the immune system (immunosuppressive) and can therefore be harmful to an individual's general health (Tamatam, Khanum & Bawa, 2012). This is also evidenced by the presence of glucocorticoid hormones in response to stress which are

thought to be immunosuppressive. Other immune biomarkers such as altered neuroendocrine function and inflammatory cytokines have been reported in depressed samples (Tamatam, Khanum & Bawa, 2012). This indicates that stress plays a role a role in reducing the efficacy of the immune system in individuals with depression.

The hypothalamic-pituitary-adrenal (HPA) axis incorporates all the major components involved in a stress response and is therefore an important target for study in depressed samples. The HPA axis is made up of the hypothalamus, the anterior pituitary and adrenal cortex (Roy & Campbell, 2013). In response to stress, the HPA axis facilitates the release of several hormones, namely corticotrophin releasing hormone and adrenocorticotrophic hormone. These hormones mediate the release of corticosteroids including glucocorticoids and cortical sex hormones (Roy & Campbell, 2013). Glucocorticoids include the stress hormone cortisol which when released results in a series of physiological processes aimed at increasing blood glucose and suppressing immune function. These processes are thought to prepare the body for stress and are regulated by a negative-feedback system (Roy & Campbell, 2013).

Excessive levels of cortisol and other related hormones inhibit HPA axis activity in order to keep the system functioning and regulated (Roy & Campbell, 2013). However, continuous elevation of stress hormones impairs this negative-feedback system (Roy & Campbell, 2013). In a subset of individuals with depression, hyperactivity of the HPA axis has been observed indicating that during a depression episode the body is in a biological state of stress. Other conditions, such as Cushing's syndrome and thyroid disorders, are also associated with impaired HPA axis regulation and are common co-morbid conditions with depression providing support for impaired HPA axis regulation in depression (Roy & Campbell, 2013). Biopsychosocial models of depression, reviewed in the next section, address the role of stress in the pathophysiology of depression.

1.6.6 Biopsychosocial models. Proposed casual factors of depression can be characterised into either biological, psychological or psychosocial factors which when integrated together become a biopsychosocial model of depression. Biopsychosocial models acknowledge that depression has both a biological and social aetiology (Roy & Campbell, 2013). The efficacy of combined pharmacological and psychological treatments for depression provides support for an integrated model of depression (Schotte et al., 2006). In addition to biological, psychological and social factors the integrated biopsychosocial model also incorporates environmental and stress factors in the aetiology of depression (Schotte et al., 2006). One of the most prominent biopsychosocial models is the diathesis-stress model. Diathesis refers to both the biological and psychosocial vulnerabilities to depression such as early life experiences, genetics, cognitions and personality (Willner, Scheel-Kruger & Belzung, 2013). Individual differences in genetic predisposition and inherent

vulnerabilities to depression, in combination with individual differences in stress exposure, result in fluctuating levels of symptom severity and variation in the degree of risk in developing depression (Patten, 2013). According to Willner, Scheel-Kruger and Belzung (2013), as an individual's diathesis (vulnerability to depression) increases, the level of stress needed to precipitate an episode of depression decreases. In chronic or recurrent depression, the occurrence of one depression episode increases the diathesis for future episodes (Willlner, Scheel-Kruger & Belzung, 2013).

There are individual differences in diathesis strength (vulnerability) which influences whether or not depression will occur (Willner, Scheel-Kruger & Belzung, 2013). For example, an individual with a weak diathesis may only develop depression in the face of intense stress whereas an individual with a strong diathesis will develop depression in response to minor stressors (Willner, Scheel-Kruger & Belzung, 2013). In line with stress sensitisation or "kindling" theory, as the diathesis increases over time due to recurrent episodes and genetic risk, the strength of the required stressor to precipitate an episode of depression decreases (Willner, Scheel-Kruger & Belzung, 2013). Willner, Scheel-Kruger & Belzung (2013) propose that in individuals with a strong diathesis the recurrence of depression is almost independent of stress.

Biopsychosocial models of depression can extend to treatment selection. A combination of treatments including psychotherapy, pharmacotherapy and lifestyle modification may reduce the burden of depression. Several lifestyle factors such as diet, level of exercise, alcohol consumption and smoking have been associated with the risk of depression and are linked to co-morbid medical conditions commonly accompanying depression (e.g. heart disease) (Berk et al., 2013). Modifying these lifestyle factors may provide benefit in conjunction with traditional treatment modalities. Other psychosocial interventions such as improving social networks, peer support and increasing access to health services also contribute to reducing the burden posed by depression (Berk et al., 2013).

1.7 Treatments for Depression

The American Psychiatric Association (APA), the United Kingdom's National Institute for Health and Clinical Excellence (NICE) and the Royal Australian and New Zealand College of Psychiatrists (RANZCP) have all established clinical practice and treatment guidelines for depression in adults. The guidelines propose three main treatment modalities for depression, pharmacology, psychotherapy and somatic therapies. Clinical practice guidelines also address the benefits of alternative therapies and healthy lifestyle factors in the treatment of depression. Practice guidelines are designed using the strongest evidence-based care interventions by reviewing

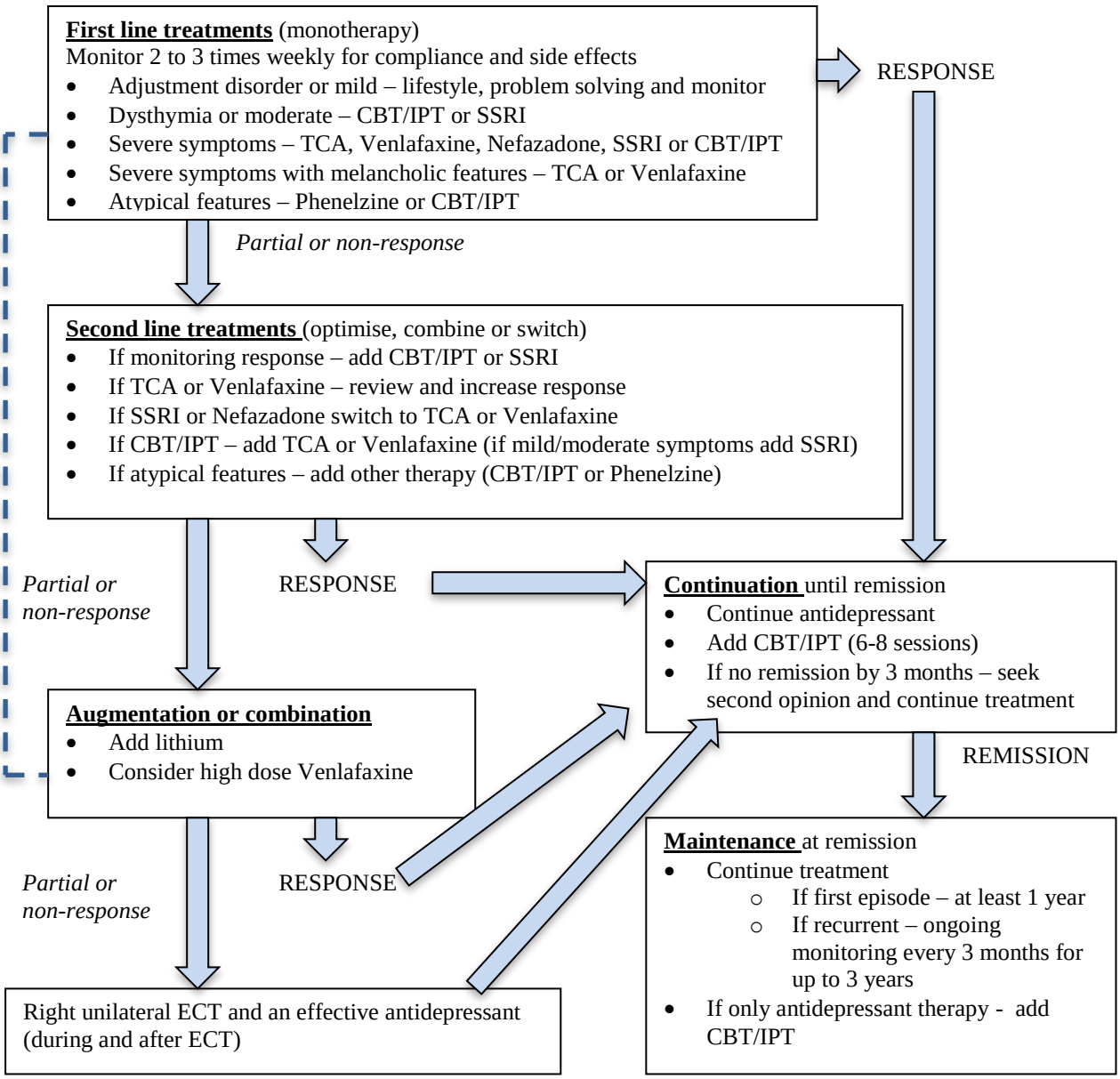
treatment outcome literature and performing meta-analyses to determine the level of empirical support for a particular treatment. This section outlines the prominent and efficacious treatments for depression in adults. Figure 1.1 presents the recommended treatment algorithm provided by the RANZCP for the treatment of depression in Australian clinical practice settings.

Treatment for depression is divided into three phases; acute, continuation and maintenance (Malhi, Hitching, Berk, Boyce, Porter, & Fritz, 2013). The acute phase of treatment aims to alleviate the symptoms of depression resulting in remission from the current episode. The goal of continuation is to prevent a relapse of symptoms leading to complete recovery. Once recovery is attained the maintenance phase aims to prevent the recurrence of a depression episode. Antidepressant medication alone, or in conjunction with psychotherapy, is the first line of treatment for the acute symptoms of depression (Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression, 2004). Antidepressants are classified into classes according to their main mechanism of action (see Table 1.3). The selection of an antidepressant is a balance between tolerability, adherence factors, efficacy and risk (Malhi, Hitching, Berk, Boyce, Porter, & Fritz, 2013). Selective serotonin reuptake inhibitors (SSRIs) are considered to be the most tolerable and safest antidepressants available and are usually the first trialled during an episode of depression (Malhi, Hitching, Berk, Boyce, Porter, & Fritz, 2013). Other antidepressants such as, tricyclic agents (TCA) and Monoamine Oxidase Inhibitors (MAOIs) have a greater side effect profile and are associated with greater risk of toxicity (Malhi, Hitching, Berk, Boyce, Porter, & Fritz, 2013). However, they are efficacious in treating certain features of depression, such as depression with melancholic and atypical features, as well as depression complicated by pain or treatment resistance (Malhi, Hitching, Berk, Boyce, Porter, & Fritz, 2013).

Practice guidelines suggest the combined use of antidepressants with psychotherapy for the treatment of depression. Cognitive behavioural therapy (CBT) is the dominant form of psychotherapy recommended for the treatment of depression. Evidence suggests that CBT alone is as effective as medication for the treatment of mild to moderate depression (Lampe, Coulston, & Berk, 2013). Other structured psychotherapies such as interpersonal therapy (IPT), acceptance and commitment therapy (ACT) and mindfulness-based cognitive therapy (MBCT) also have clinical utility in the treatment of depression (Lampe, Coulston, & Berk, 2013). The use of psychotherapy in the maintenance phase of treatment has similar efficacy to antidepressant therapy and may be a viable option in circumstances when medication is contraindicated or poorly tolerated (Lampe, Coulston, & Berk, 2013). Additionally, the response rate to psychotherapy is reported to be slower than to antidepressant medication (Lampe, Coulston, & Berk, 2013). In select populations such as

children, adolescents, pregnant or postnatal women, the delay in response is balanced by the adverse risks posed by antidepressant therapy when selecting treatment.

Treatment selection is driven primarily by clinician and patient preference (Malhi, Hitching, Berk, Boyce, Porter, & Fritz, 2013). Most individuals show response, usually a 20 to 50% reduction of symptoms on a depression rating scale, to antidepressant treatment within two to four weeks (Malhi, Hitching, Berk, Boyce, Porter, & Fritz, 2013). However, it is not uncommon for individuals to have an unsatisfactory response to treatment or for response to plateau during treatment (Malhi, Hitching, Berk, Boyce, Porter, & Fritz, 2013). Available guidelines provide treatment strategies to manage partial and non-response to treatment using optimisation, switching, augmentation and combination treatment (see Figure 1.1). Somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS) are used in the treatment of depression that is unresponsive to previous treatment or when treatment with antidepressants is not viable (Kennedy & Giacobbe, 2007).



Note. Adapted from RANZCP Clinical Practice Guidelines for depression (2004)

Figure 1.1. The RANZCP treatment algorithm devised using evidence-based treatments for depression

1.8 Treatment Settings in Australia

Depression can be treated in the community by general practitioners (GP) (primary care providers) and/or by specialists such as psychologists or psychiatrists (secondary care). Public and private inpatient treatment settings (tertiary care) are also available to treat individuals with depression. Primary care is the most common level of care utilised by community-residing Australians (Andrews, Henderson & Hall, 2001). Glozier and colleagues (2012) evaluated how depression is managed in Australian primary care and how individuals with depression access specialist care via secondary and tertiary care. During 2008, a select number of GPs (N = 200) were asked to report health service utilisation, socio-demographic and clinical data on five to seven of their patients presenting with depression (Glozier, Davenport & Hickie 2012). Approximately one in eight (12%) of the individuals presenting with depression at primary care settings required a referral to a psychologist (Glozier, Davenport & Hickie 2012). Referrals to psychiatrists were less common (Glozier, Davenport & Hickie 2012). Just over three quarters of the patients (77%) were taking antidepressants indicating that GPs manage the majority of antidepressant prescriptions (Glozier, Davenport & Hickie 2012). Patients who were under shared care (i.e. managed by a GP and psychiatrist) were more impaired than those who were just managed by a GP. In particular, individuals in shared care had a chronic illness duration, more severe symptomatology and recurrent episodes of depression (Glozier, Davenport & Hickie 2012).

Community-residing Australians who required hospitalisation in either public or private inpatient settings were examined by Draper and Low (2009) using data from the Australian Institute of Health and Welfare in the National Hospital Morbidity Database (1998/9 to 2004/5). During the investigation period, the annual rate of hospitalisation for depressive disorders was 2.6 per 1000 for men and 4.8 per 1000 for women (Draper & Low, 2009). Males and females in midlife (35 to 50 years old) or late-life (65 years old older) were most likely to be admitted to hospital for depression (Draper & Low, 2009). The majority of individuals admitted to hospital for depression were diagnosed with severe depression without psychosis (1.81 per 1000 for men and women) (Draper & Low, 2009). Individuals with less severe forms of depression were not common in inpatient settings (mild depression, .03 per 1000 for men and women; moderate depression .30 per 1000 for men and women) (Draper & Low, 2009). From the data presented by Glozier and colleagues (2012) and Draper and Low (2009) it can be inferred, that if treatment is sought (as not all individuals will seek treatment), mild depression is most commonly treated by a GP in primary care and moderate to severe depression is treated in shared care by a GP and specialist (either in hospital by a psychiatrist or as an outpatient by a psychiatrist or psychologist).

It is expected that a proportion of community-residing Australians self-manage their depression and do not seek treatment. Estimates from the medical scientific literature report that up to 50% of individuals with depression do not seek treatment (Gulliver, Griffiths & Christensen, 2012). The reasons for low help seeking in individuals with depression and other mental health problems are varied and include gender, income, access and perceived need for help (Gulliver, Griffiths & Christensen, 2012). Factors which have been associated with higher help seeking and greater use of mental health services in community-residing Australians are being female, separated or divorced, having a higher level of education, being on a government pension and unemployment (Mills et al., 2012; Parslow & Jorm, 2000). A main factor which predicts help seeking and the use of mental health services is physical health problems (Mills et al., 2012; Parslow & Jorm, 2000). For an individual, being an active consumer of the general healthcare system results in greater mental health service use due to the interrelatedness between mental and physical conditions. Social factors including access and affordability, cultural appropriateness, remoteness and perceived need for services are also considered barriers to help seeking (Mills et al., 2012).

In an Australian study of adults who were non-treatment seeking (N = 822) the factors predicting access to mental health services were assessed (Mills et al., 2012). In line with previous studies (Mills et al., 2012; Parslow & Jorm, 2000), perceived need was the strongest factor in predicting service use. Current psychological distress measured by the SPHERE, general health complaints and alcohol dependence were also predictors of help seeking and access to mental health services in previously non-treatment seeking members of the community (Mills et al., 2012). More specifically, seeking help from a GP was associated with the presence of a mood disorder, being female, a greater number of physical health complaints and an older current age (Mills et al., 2012). In previously non-treatment seeking adults, access to specialist care (i.e. psychiatrists and psychologists) was associated with higher levels of disability, greater levels of childhood trauma, as well as, being female and divorced (Mills et al., 2012).

Many factors contribute to the level of health service utilisation of individuals with depression in the community. The recurring or common factors associated with help seeking are being female, physical health complaints, more severe symptoms, psychological distress and a perceived need for help. The emergence of childhood adversity as a predictor for specialist care highlights the need for early community intervention (Mills et al., 2012). Early adversity and multiple co-morbidities in community members accessing higher level mental health services emphases the complex presentations seen in secondary and tertiary care settings.

1.9 Efficacy of Antidepressant Therapy

During the late nineteenth and early twentieth century, the primary treatments for a depressive illness were electroconvulsive therapy (ECT), opium, warm baths and institutionalisation (Ban, 2014). A recent systematic review of outcome studies (N = 29) of patients with mood disorders treated with ECT prior to the widespread use of pharmacotherapy (studies published before the 1970s were included) report the median rate of recovery and remaining well at follow-up was 51% (Mulder & Frampton, 2014). This rate is thought to be similar to, or even slightly higher than, contemporary recovery rates (Mulder & Frampton, 2014). Other studies, such as Kiloh, Andrews and Neilson (1988) and Lee and Murray (1988), which assessed the outcomes for patients with depression during the 1960s and 1970s, found that long-term outcomes for patients with depression were poor, with only 20% of patients remaining well over a 15-year follow-up. These historical studies emphasise the poor long-term outcomes of patients with depression and highlight that our treatments have not significantly improved the outcome for patients over time.

A contemporary systematic review of the efficacy of treatments for depression assessed clinical trial data from the United States Food and Drug Administration (US FDA) and medical scientific literature between 1975 and 2009 (Khan et al., 2012). This study compared the efficacy of the following treatments for depression: 1) combination psychotherapy and antidepressants; 2) antidepressants only; 3) psychotherapy only; 4) alternative therapies (including exercise and acupuncture); and 5) control treatment groups (including placebo controls and wait-list controls) (Khan et al., 2012). A total of 115 depression trials were reviewed and trials needed to report the reduction in symptom severity to be included. The combination of antidepressants with psychotherapy provided the greatest reduction in symptom severity when compared to other interventions (Khan et al., 2012). Antidepressant treatment trials published in medical scientific literature had a percentage symptom reduction rate of 51% and resulted in greater symptom reduction when compared to placebo (Khan et al., 2012). However, unsuccessful and unpublished clinical trial data available from the US FDA had a lower symptom reduction rate of 42% for antidepressant trials, indicating that antidepressants may not as effective as reported in medical scientific literature (Khan et al., 2012).

Unsuccessful antidepressant trials are not usually published, resulting in an inflated efficacy rate (Pigott, Leventhal, Alter & Boren, 2010). The issue of publication bias has been widely acknowledged, with calls for more standardised research into whether particular presentations of depression are more likely to respond to a particular treatment modality (see Pigott, Leventhal, Alter & Boren, 2010). This was one of the main aims of STAR*D, the largest multi-centre study of treatments for depression to date (see section *1.10.1 STAR*D*).

Despite the methodological differences between studies using historical and contemporary samples, the rates of recovery and symptom reduction suggest that modern treatments for depression may not have improved the outcomes of patients with mood disorders (Mulder & Frampton, 2014). According to Khan et al., (2012) depression as it is currently conceptualised may be too broad and heterogeneous to treat in a homogenous manner. It has been argued that targeting treatments for particular symptom profiles, patient characteristics (e.g. age, gender, weight) and biomarkers should be considered along with research focused at developing a more appropriate diagnostic conceptualisation of depression (Khan et al., 2012).

1.10 What is Treatment-Resistant Depression (TRD)?

Refractory or treatment-resistant depression (TRD) refers to depression that is non-responsive to treatment. The term "treatment-resistant depression" first appeared in medical scientific literature in the 1970s and has superseded "refractory depression" as the overarching label for non-response to treatment. The burden of depression is increasing (Lepine & Briley, 2011) despite advancements in the safety and tolerability of treatments for depression over the past 50 years. Our current armamentarium of treatments for depression may not be as successful or efficacious as reported in randomised controlled trials (RCTs). There are long-standing concerns about publication biases which inflate the perceived efficacy of antidepressants in RCTs and inadvertently influence evidence-based care for individuals with depression (Pigott, Leventhal, Alter, & Boren, 2010; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). In an attempt to rectify the reporting of the efficacy of antidepressants, the National Institute of Mental Health (NIMH) funded the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study using a community representative sample of outpatients with MDD.

1.10.1 Sequenced Treatment Alternatives to Relieve Depression study (STAR*D). The primary aim of the STAR*D study was to fill "major clinical information gaps and to evaluate the theoretical principles and clinical beliefs that currently guide" the treatment of depression (Fava, et al., 2003a). A representative sample of patients and settings was sourced to assess the clinical management of patients in real world situations (Fava, et al., 2003a). The STAR*D study assessed the effectiveness of treatments for depression when remission was not attained from an initial trial of an SSRI in outpatients with DSM-IV MDD (N = 4041). The assignment of subsequent treatment levels following non-response to the initial trial of an SSRI was randomised. A 12-month naturalistic follow-up was included to determine the incidence of relapse and recurrence in the sample.

Only treatment seeking patients, aged between 18 and 75 years old with a diagnosis of DSM-IV MDD were enrolled in the initial treatment trial of citalopram (N = 4041). Of the enrolled participants who completed the initial treatment trial of citalopram (N = 3671), 62.2% were female with a mean age of 40.7 years (SD = 13.2 years) and mean education years of 13.5 (SD = 3.2 years) (Rush et al., 2006b). Table 1.4 summarises the treatment levels initiated by the STAR*D study. The primary outcome measures were the 17-item Hamilton-Rating Scale for Depression (HAM-D) and the 16-item Quick Inventory of Depressive Symptomatology- Self-report (QIDS-SR) (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Response was defined as 50% or higher reduction in baseline QIDS-SR score and remission was defined as a score of 7 or less on the HAM-D (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Patients who were intolerant of or who showed an inadequate response to citalopram were able to enter Level 2 (N = 1439). Patients who experienced an inadequate response to treatment in Level 2 were enrolled in Level 3 (N = 377). Finally, patients with an inadequate response to treatment in Level 3 participated in Level 4 (N = 109).

The remission rate was approximately 37% for Level 1, 31% for Level 2, 14% for Level 3 and 13% for Level 4. Furthermore, the relapse rate of patients increased with each subsequent level of treatment from 58.7% for Level 1, 67.7% for Level 2, 76% for Level 3 and 83.3% for Level 4. Thus, as further treatment strategies were trialled the rate of response and remission diminished (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Patients who were classified as treatment resistant (entered higher levels of treatment) had a greater medical illness burden, longer depression episode duration and a higher mean 17-item HAM-D score at baseline (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). The STAR*D study found that remission rather than response to treatment should be the preferred goal of treatment as remission at any level of the study was associated with a lower risk of relapse at the 12-month follow-up in comparison to individuals not in remission (showing no response or response without remission) (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007).

To date, the STAR*D study provides the most compressive and representative view of the non-response of treatment for depression. Utilising a representative sample the STAR*D highlights the lower than expected efficacy of treatments for depression and the need for sequential treatments following the non-response to initial treatment in a majority of patients with depression (Gaynes, Warden, Trivedi, Wisniewski, Fava, & Rush, 2009). A further implication of the STAR*D study was the acknowledgement that patients with chronic or recurrent episodes of depression require a greater number of treatment strategies to potentiate response and have poorer long-term outcomes (Gaynes, Warden, Trivedi, Wisniewski, Fava, & Rush, 2009).

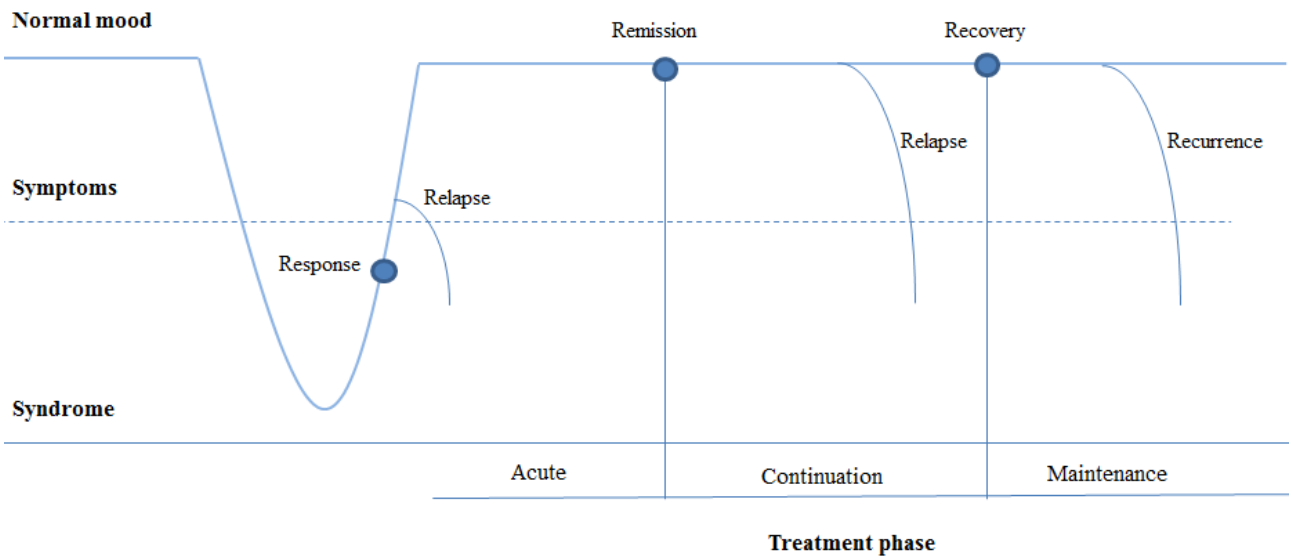
Table 1.4

*STAR*D study treatment levels*

Treatment level	Strategy (12 to 14 weeks)
Level 1	Citalopram
Level 2	Switch to either o Sertraline o Bupropion-sustained release o Venlafaxine-extended release o Cognitive therapy OR Augmentation of citalopram with either o Bupropion-sustained release o Buspirone o Cognitive therapy
Level 3	Switch to either o Mirtazapine o Nortriptyline OR Augmentation of Level 2 treatment with either o Lithium o Thyroid hormone (T_3)
Level 4	Switch to either o Tranylcypromine (MAOI) o Combination of Venlafaxine-extended release with mirtazapine

1.10.2. The Six R's of treatment outcomes. There are several points across the depression illness course which mark the change in duration and severity of symptoms in response to treatment (Conradi, Ormel & de Jonge, 2012). These points are widely used in research and clinical practice but are inconsistently defined and not empirically validated (Conradi, Ormel & de Jonge, 2012). In the late 1980s and early 1990s there was a call for consensus on the terms and definitions used to define transitional points across the illness course. Frank et al. (1991) summarised the need for the consensus reporting that empirical validation and consistent conceptualisation of these terms would aid the interpretation and comparison of observational studies and clinical trials, clarify the relationship between psychological and biological aetiologic factors, improve treatment guidelines,

guide empirically based revisions of the diagnostic criteria and provide consistency when evaluating new treatments and therapies for depression. In 2006 the American College of Neuropsychopharmacology (ACNP) created a task force to provide recommendations on the conceptualisation of treatment outcome terminology. The ACNP Task Force acknowledged that the recommendations and definitions provided were atheoretical and lacking empirical evidence (Rush et al., 2006a). The following six terms are commonly employed to refer to points across the depression illness course and are defined by the ACNP as a guide for researchers and clinicians. Figure 1.2 visually displays the treatment outcome points across the illness course.



Note. Adapted from Kupfer (1991).

Figure 1.2. Treatment outcomes across the depression illness course

How treatment outcomes and transitional points across the illness course are defined directly influence how TRD is conceptualised. Inconsistent and atheoretical definitions of treatment outcomes are carried through to the conceptualisation of TRD. This is because current definitions of TRD are reliant on predetermined symptomatology cut-offs and response criteria. Thus the need to conceptualise and empirically validate points across the depression illness course is paramount in order to adequately conceptualise and standardise the phenomenon of TRD.

1.10.2.1 Response. Broadly, response is defined as a "clinically meaningful degree of symptom reduction" which is accompanied by an improvement in functioning and mood (Rush et al., 2006a). Response is an important concept for both patients and clinicians as it can guide whether or not to continue treatment, adjust the dose, add adjunctive treatment or switch to another

treatment modality (Rush et al., 2006a). Historically, response has often been defined as a 50% or more reduction in baseline symptomatology on depression rating scales (Rush et al., 2006a). In treatment resistant samples, a decrease of 50% or more in baseline symptom severity may not be achievable (Rush et al., 2006a). A more realistic determination of response in treatment resistant samples could be a 25% or more reduction in symptomatology (Rush et al., 2006a). The ACNP Task Force highlighted the need to consider the initial presentation (e.g. level of treatment resistance and symptomatology) when defining specific response criteria.

In order to reduce the effect of symptomatic fluctuations and variations in symptomatology ratings, the ACNP Task Force recommended that response criteria be met for 3 weeks. The required time period to sustain response is a guide to clinicians and researchers and may not be attainable by all depressed samples (Rush et al., 2006a). There may be marked differences in reduction of symptomatology and how long response is sustained between chronic and TRD samples compared to acutely ill or first episode presentations. The ACNP Task Force definition of response (sustaining a 50% reduction in baseline symptomatology over 3 weeks) is a guide only and its implementation most likely varies between depressed populations and between clinicians. Unstandardized treatment paradigms and response criteria impede the ability to empirically validate the concept of response and are consequently reflected in higher-order treatment outcome conceptualisations, like TRD. Chapter Two systematically reviews the conceptualisation of TRD in medical scientific literature.

1.10.2.2. Remission. The ACNP Task Force defines remission as the absence of depression symptoms and the return to normal functioning (Rush et al., 2006a). The definition of remission can be used in non-treated as well as treated samples. In order to achieve remission status, the symptoms of depressed mood or anhedonia cannot be present and no more than three of the other seven depression symptoms can be present (e.g. poor concentration, disrupted sleep, appetite changes, reduced motivation etc.). This is a theoretically based threshold and has not been empirically validated. The ACNP Task Force, recommend using the core symptoms of depression over depression rating scales to define remission. The rationale behind this recommendation is that depression is a "hedonic deficit" which is conceptualised by the two core symptoms of depression (depressed mood and anhedonia) (Rush et al., 2006a). The disorder is not completely resolved if either of these symptoms are still endorsed. There is an inherent problem with this definition given that it does not mean the complete absence of depression symptoms. Additionally, this definition of remission fails to incorporate other factors associated with wellness such as occupational functioning, day-to-day functioning and physiological changes (Israel, 2010). However, the complete absence of symptoms is difficult to achieve with at least half of patients still experiencing

at least two or more residual symptoms after remission is designated (Nierenberg et al., 2010). Like the conceptualisation of depression more generally, the criteria used to define remission and response is are atheroretical and consensus driven. It is therefore expected, due to continued atheoretical conceptualisations and lower than expected treatment efficacy, that our current definition of remission does not capture the complete resolution of the disorder.

Like response, the absence of depression symptoms should be sustained for 3 weeks before designating remission status (Rush et al., 2006a). The state of remission is more likely to persist once this 3-week period has been sustained (Rush et al., 2006a). Remission rather than response is the ideal goal of treatment (Rush et al., 2006a). Complete remission in comparison to the presence of residual symptoms results in better functioning and long-term outcomes (Rush et al., 2006a).

1.10.2.3 Residual symptoms. The ACNP Task Force refer to residual symptoms as sub-syndromal symptoms. Both of these terms refer to the presence of depression symptoms but not the required number of symptoms (five out of nine) or severity/duration to meet diagnostic criteria. The presence of residual symptoms has been associated with poorer long term outcomes and significant functional impairment in treated patients who responded to treatment (cited in Romera et al., 2013). Remitted patients from the STAR*D project were more likely to relapse if they had a greater number of residual symptoms (Nierenberg et al., 2010). The STAR*D project reports more than 90% of patients who remitted had at least one residual depression symptom (Nierenberg et al., 2010). The most common residual symptom domains in remitted STAR*D patients were sleep disturbance and appetite changes (Nierenberg et al., 2010). There is strong evidence to suggest the presence of residual symptoms results in poorer outcomes and predicts the recurrence or relapse of depression. Likewise, patients who achieve remission with very few residual symptoms are likely to experience more favourable outcomes and are less likely to have a relapse or recurrence (Nierenberg et al., 2010). Thus the primary goal of treatment is complete symptomatic remission and ongoing management of residual symptoms to prevent relapse or recurrence.

1.10.2.4 Recovery. Recovery is defined as "an extended period of remission" (Rush et al., 2006a). According to the ACNP Task Force, during the recovery phase an episode of depression is "unlikely to occur" (Rush et al., 2006a). Recovery can be designated regardless of treatment status. When recovery is obtained, current treatment can be discontinued (Rush et al., 2006a). The ACNP Task Force recommended that recovery is designated once remission status has been sustained for at least 4 months (Rush et al., 2006a). This cut-off was based on naturalistic and clinical trial data which report the increased likelihood of relapse within the first 4 months of the year following remission (Rush et al., 2006a). If symptoms reoccur during this period "recurrence" is ascribed. If

the symptoms are sub-threshold and do not meet criteria for a depression episode, the term "sub-syndromal symptoms following recovery" should be designated.

***1.10.2.5 Recurrence and Relapse*.** The terms recurrence and relapse refer to the return of a depression episode and is not to be confused with residual or sub-syndromal symptoms (Rush et al., 2006a). The difference between recurrence and relapse is that relapse occurs before recovery during the remission phase and recurrence occurs after recovery (Rush et al., 2006a). In both instances, recovery and relapse, criteria for a depression episode must be met (Rush et al., 2006a). The presence of residual or sub-syndromal symptoms does not indicate a recurrence or relapse and should be monitored for during the recovery and remission phase (Rush et al., 2006a). The ACNP Task Force recommends further research to determine the clinical significance of residual or sub-syndromal symptoms during recovery and remission phases. Currently, there is not a clear consensus on whether the presence of residual or sub-syndromal symptoms during remission or recovery increases the likelihood of relapse and recurrence and whether these symptoms impact daily functioning (Rush et al., 2006a).

1.10.3 Prevalence of TRD. The lack of a standardised definition of TRD without a systematic way to identify the phenomenon in clinical practice and research has made prevalence estimates of TRD difficult (Nemeroff, 2007). Current prevalence estimates differ depending on the employed definition of TRD. Additionally, prevalence estimates are dependent on the treatment setting and study design used. In particular, the definition of response, remission and treatment adequacy differ between studies and result in inconsistent reporting of the prevalence of TRD. Not surprisingly, lower levels of TRD are reported in primary care settings whereas higher rates of TRD occur in inpatient psychiatric settings (Nemeroff, 2007).

In depressed outpatients, the STAR*D reports a cumulative remission rate of 50% after two different treatments are trialled (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007; Gaynes, Warden, Trivedi, Wisniewski, Fava, & Rush, 2009). This finding provides empirical support for the most commonly employed definition of TRD, the failure of two antidepressant trials (Berlim & Turecki, 2007b).

1.10.4 Staging models of TRD. Five staging models of TRD (Appendix 1) have been developed to classify and identify TRD in clinical practice and research (Fekadu, Wooderson, Markopoulo, Donaldson, Papadopoulos, & Cleare, 2009b; Fava, 2003a; Souery, et al., 1999; Thase & Rush, 1997; Oquendo, et al., 2003; Sackeim, Prudic, Devanand, Decina, Kerr, & Malitz, 1990). These models also aim to standardise the conceptualisation of TRD by including definitions of treatment adequacy and/or treatment failure (Nemeroff, 2007). However, the available staging models of TRD have not been appropriately validated and no model has been adopted for

widespread use (Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012). Models of TRD stage TRD arbitrarily and were developed based on anecdotal impressions and algorithms of experience and expertise rather than empirical data (Trivedi et al., 2006). This approach was necessary as empirical data do not exist and the phenomenon of TRD remains ambiguous and atheoretical (Trivedi et al., 2006). It should be noted that current definitions and conceptualisations of TRD are systematically reviewed in the following chapter (Chapter Two) and will not be discussed in any further detail in this chapter.

1.10.5 The economic and human burden of TRD. The phenomenon of TRD has been associated with a large economic and disease burden. Patients with TRD accrue high levels of healthcare expenditure and health service utilisation (Olchanski, McInnis Myers, Halseth, Cyr, Bockstedt, Goss, & Howland, 2013; Crown, et al., 2002; Fostick, Silberman, Beckman, Spivak, & Amital, 2010). Loss of productivity due absenteeism and poor occupational functioning in TRD patients also contributes to the high economic burden posed by TRD (Greenberg, Corey-Lisle, Birnbaum, Marynchenko, & Claxton, 2004; Ivanova, Birnbaum, Kidolezi, Subramanian, Khan, & Stensland, 2010).

A systematic review (N = 9) of the medium to long-term outcomes in TRD associates treatment resistance with a highly recurrent course, poor quality of life and increased mortality (Fekadu, Wooderson, Markopoulo, Donaldson, Papadopoulos, & Cleare, 2009b). Recent outcome studies confirm poorer outcomes in patients with TRD. A cohort of TRD patients (N = 84 unipolar; N = 31 bipolar) were followed-up 3.3 years post discharge from a tertiary unit in the United Kingdom to determine the long-term course of TRD (Vergunst, et al., 2013). More than one third of patients (39%) remained symptomatic as indicated by an unremitting chronic course during the follow-up period (Vergunst, et al., 2013). In line with findings from the STAR*D study, residual symptomatology and non-remission post-treatment is associated with poorer longer outcomes in TRD (Fekadu, Wooderson, Rane, Markopoulou, Poon, & Cleare, 2011). This was confirmed by a recent study which followed-up (median 3 years) 118 patients with TRD post inpatient treatment in the United Kingdom (Fekadu, Wooderson, Rane, Markopoulou, Poon, & Cleare, 2011). Patients with TRD discharged in remission (N = 40; 37%) spent less time in an episode of depression, had a significantly less severe illness and better functional outcomes at follow-up (Fekadu, Wooderson, Rane, Markopoulou, Poon, & Cleare, 2011).

In summary, high levels of recurrence and chronicity are characteristic of the TRD illness course (Fekadu, Wooderson, Markopoulo, Donaldson, Papadopoulos, & Cleare, 2009b; Vergunst, et al., 2013). Residual symptoms and non-remission post-treatment predict poorer outcomes in patients with TRD (Fekadu, Wooderson, Markopoulo, Donaldson, Papadopoulos, & Cleare, 2009b).

In particular, the chronic and unremitting nature of TRD results in high levels of disability and mortality in the long-term (Fekadu, Wooderson, Markopoulo, Donaldson, Papadopoulos, & Cleare, 2009b).

1.11 Chronic Depression versus TRD

As highlighted in previous sections, depression is acknowledged to be chronic and unremitting in a substantial proportion of patients. Unlike TRD, chronic depression is diagnosable and has a fairly stable conceptualisation. In the broadest sense chronicity in depression is defined as an illness duration greater than two years (Klein., 2010). In the DSM-IV-TR chronic depression could be specified as a feature of MDD or could be diagnosed as Dysthymic Disorder (American Psychiatric Association, 2000). The diagnosis of DSM-IV-TR Dysthymic Disorder is defined as a less severe form of MDD and requires no MDE within the first two years of the disorder (American Psychiatric Association, 2000). Dysthymic Disorder and the chronic specification for MDD criteria have been removed from the DSM-5 and have been replaced with Persistent Depressive Disorder. The presence of a MDE within the first two years of illness will no longer exclude individuals from a diagnosis of Persistent Depressive Disorder.

In comparison with non-chronic depression (illness duration less than two years), chronic depression states have been associated with an earlier age of onset (Angst, Gamma, Rossler, Ajdacic, & Klein, 2009; Klein, Shankman, & Rose, 2006; Mondimore, et al., 2007), higher rates of co-morbidity (Angst, Gamma, Rossler, Ajdacic, & Klein, 2009; Gilmer, et al., 2005; Satyanarayana, Enns, Cox, & Sareen, 2009), higher rates of suicidality (Gilmer, et al., 2005; Mondimore, et al., 2007; Satyanarayana, Enns, Cox, & Sareen, 2009) and lower response rates to treatment (Keller, McCullough, Klein, Arnow, Dunner, & Gelenberg, 2000). Greater health service utilisation and disability have also been associated with chronic depression (Satyanarayana, Enns, Cox, & Sareen, 2009). The prevalence and correlates of chronic depression are detailed in Chapter Four.

Untangling the concepts of chronic depression and TRD is not easy. The phenomenon of TRD includes depression which is often chronic and unremitting just as chronic depression can be resistant to treatment. However, chronicity is not necessarily a trait marker for TRD. Findings from the STAR*D show that it is possible to trial and fail four treatment strategies within a 12-month period (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). The primary distinguishing feature of chronic depression was its association with a milder symptom severity. However the re-conceptualisation of persistent depression in the DSM-5, which allows the presence of MDE in conjunction with a chronic illness trajectory, may see the notion of chronic depression as a milder

form of depression disappear. This may result in a conceptual collapse of chronic depression and TRD into the DSM-5 diagnosis of Persistent Depressive Disorder.

The study of chronic depression and TRD is complicated by variations in the conceptualisation of both phenomena and by heterogeneous research methodology. The DSM-5 diagnosis of Persistent Depressive Disorder is so recent that epidemiological data for the disorder do not exist. In addition, variations in definition, sampling and study design have lead to inconsistent reporting of the correlates and prevalence of TRD. The non-response to treatment due to inadequate treatment, misdiagnosis, poor treatment adherence and intolerance to treatment has complicated the study of TRD. These factors labelled, pseudo-resistance, together with individual clinician biases, lack of measurement-based care, and patient heterogeneity all add to the overall phenomenon of TRD making it difficult to study in a consistent manner. With this in mind, this thesis aims to address some of the shortcomings of the extant TRD literature to improve understanding of this important condition.

1.12 Aims and Overview of Thesis

Meta-analyses and systematic reviews of treatment trials for depression have shown that depression is not always as treatable or responsive to treatment as traditionally thought (Kirsch et al., 2002; Khan et al., 2012; Pigott, Leventhal, Alter & Boren, 2010). Furthermore, there is now a clear consensus that depression is commonly a chronic disorder rather than an episodic one (Katon, Unutzer & Russo, 2010). The long-term outcome of depression is often poor, with depression coming in second behind lower back pain as the leading cause of global disability burden (Ferrari et al., 2013).

The failure to adequately treat depression is likely multifactorial and involves methodological issues surrounding how depression is diagnosed and studied, various aetiologic factors, heterogeneous presentations and unstandardised treatment regimens. Investigating the differences between those who respond to treatment and those who do not, as well as the differences between those who experience episodic rather than chronic symptoms may provide much needed information on depression illness course and help to guide appropriate treatment selection. However, this research is impeded by inconsistent conceptualisations of treatment response and what constitutes resistance to treatment. It is difficult to study the differences between two populations (for example, resistant vs. non-resistant or chronic vs. non-chronic) when the populations are continually changing depending on the definitions used, research methodologies employed, diagnostic criteria and clinician biases. Attempts at standardising or empirically

validating definitions of treatment resistance have not been successful to date. Numerous definitions and models of TRD have been put forward in the medical scientific literature but not one definition or model has been universally adopted for widespread use by researchers and clinicians. It has also been difficult to estimate the prevalence of TRD and determine the extent of the phenomenon in the community and clinical care settings. The majority of research on TRD comes from clinical trial data. Naturalistic studies on the phenomenon are less common.

Against this background, the primary aim of the thesis is to investigate the conceptualisation and correlates of chronic and treatment-resistant depression with a particular focus on the phenomenon of TRD. The thesis progresses from the macro level, reviewing the conceptualisation of TRD in medical scientific literature, to identifying chronic depression in the Australian community using epidemiological data, and then funnels down to the micro level by exploring the phenomenon of TRD in an inpatient setting. Three distinct methodological approaches were employed to examine this complex phenomenon: 1) systematic review; 2) analysis of epidemiological data on chronic depression; and 3) analysis of clinical data on depressed inpatients rated with TRD (see Table 1.5).

1.13 Research Questions

Several research questions were devised to address the overarching thesis aim using three main research methodologies: systematic review; epidemiological data; and clinical data. Table 1.5 lists the specific research questions addressed in each empirical chapter of the thesis. Due to the major heterogeneity surrounding the concept of TRD, Chapter Two systematically reviews current definitions and conceptualisation of TRD (see Research Question 1). To my knowledge, this is the largest systematic review of its kind assessing the conceptualisation of TRD and how patients in clinical practice and clinical trials are identified as treatment resistant. In Chapter Two, I systematically review the conceptualisation of TRD in medical scientific literature by retrieving definitions of TRD from the earliest reported randomised control trial (RCT) of treatments for TRD to the present day. Reviewing RCTs provides the most rigorous assessment of TRD in the medical scientific literature. These RCTs have generated five staging models with the primary purpose of identifying and staging patients with varying levels of TRD. However, the validity of these models has not been simultaneously tested on the same treatment-resistant patient sample.

Due to the ambiguity surrounding the concept of TRD, the prevalence of TRD has been difficult to estimate. In Chapter Four, I attempt to identify how prevalent TRD is in the Australian community utilising data from the *National Survey of Mental Health and Wellbeing 2007*

(NSMHWB). The 2007 NSMHWB methodology is detailed in Chapter Three. Although there were insufficient treatment data collected by the 2007 NSMHWB to allow enumeration of community-residing Australians with TRD, it was possible to identify individuals with chronic depression. As a consequence, the survey did contain variables relevant to the new DSM-5 diagnosis of Persistent Depressive Disorder. It also allowed investigation of health services utilisation by individuals with chronic depression. The second research question was designed to determine the prevalence of chronic depression among community-residing individuals and to investigate how chronic depression differs from non-chronic depression (see Table 1.5). Material from a published paper by the candidate is incorporated in this chapter, which is the first paper to provide epidemiological data on DSM-5 Persistent Depressive Disorder in the Australian community.

Individuals with chronic depression are not necessarily treatment-resistant. A proportion of community-residing individuals with chronic depression are untreated, self-manage their depression or do not conceptualise their symptoms as depression. Using data from the 2007 NSMHWB it was possible to assess the differences in health services utilisation between individuals with chronic depression and identify the factors related to untreated chronic depression and high levels of health services utilisation (e.g. tertiary and secondary care). It could be inferred that high levels of health services utilisation in chronically depressed community-residing Australians may indicate a degree of TRD. Previous research indicates that tertiary care settings manage more severe and complex presentations of depression (see *1.8 Treatment settings in Australia).* Thus, Research Question 3 was designed to assess whether chronically depressed community-residing individuals who accessed higher-level health services (i.e. tertiary care settings) are more likely to have a complex presentations and experience TRD.

As TRD is likely to be treated by higher-level health services, a sample of depressed inpatients was recruited from a private hospital in Brisbane, Australia to determine the degree of TRD in higher-level health services (Research Question 4). The research methodology is outlined in Chapter Five. The depressed inpatient sample was assessed for TRD using the available staging models (see *1.10.4 Staging models of TRD*). In Chapter Six, I assess how the five staging models of TRD are related and whether they rate TRD in a similar way. A composite index of TRD is developed in order to capture the level of agreement between the models. This composite index of TRD is compared to the definition of TRD as the failure of three or more antidepressants to determine whether the models of TRD provide any additional exploratory power above and beyond what is provided by a basic dichotomous definition of TRD (see Research Question 5). There was insufficient power to use the failure of two antidepressants as the definition of TRD as over 75% (N = 54; 77.1%) the inpatient sample had failed more than two antidepressants over their lifetime. This

finding should be considered in the context of not being able to determine the adequacy of each treatment trial due to missing data on key variables such as dose, duration and response. Therefore the failure of three or more antidepressants was used as the dichotomous definition tested. Comparing a dichotomous definition of TRD to a continuum rating may provide evidence of the clinical utility of the TRD models and support the notion that dichotomous definitions of TRD are too broad to have any meaningful clinical significance. To my knowledge, this is the first study to compare all five staging models in the one patient sample in order to test the level of agreement between the models and their usefulness at identifying and staging TRD.

Personality factors associated with TRD have rarely been studied and therefore the final empirical chapter aims to uncover whether there is an association between personality and treatment resistance (see Research Question 6). The sixth research question was addressed utilising the sample of depressed inpatients described in Chapter Six. Firstly, the depressed inpatient personality ratings are compared to informant ratings of the inpatient personality ratings to determine whether the inpatient ratings are valid and not dependent on their current depressed state. Afterwards, the inpatient personality ratings are compared to an independent sample of healthy controls (never been depressed) and previously depressed outpatients with supposedly better treatment outcomes to assess whether depressed inpatients have a different underlying personality structure. Finally, personality variables and relevant clinical and socio-demographic factors are explored as predictors of TRD using a newly created composite index of TRD as the outcome variable to assess whether personality plays a role in treatment resistance.

Table 1.5

Thesis Structure and Research Questions

Chapter	Chapter content/Research Question (RQ)	Methodology
One	**Introduction**	N/A
Two	**A systematic review of the conceptualisation of TRD** **RQ 1:** How is treatment resistant depression (TRD) identified and conceptualised in the medical scientific literature?	Systematic Review
Three	**Research Methodology A**	Epidemiological data
Four	**Chronic depression in the Australian community** **RQ2:** What is the prevalence of chronic depression in community-residing individuals and what factors are associated with chronic depression in this population? **RQ3:** Are community-residing individuals with chronic depression who utilise higher level health services (i.e. those seen in tertiary care settings) more likely to exhibit characteristics associated with TRD (such as displaying a more chronic and complex presentation) than those with chronic depression who remain untreated or who use lower levels of health services (i.e. those seen in primary and secondary care settings)?	Epidemiological data
Five	**Research Methodology B**	Clinical data
Six	**The degree of TRD in a tertiary care setting** **RQ4:** What is the degree of treatment resistance, as measured by TRD staging models, in a sample of depressed inpatients? **RQ5:** What factors predict TRD using a composite index of TRD compared to the definition of the failure of three or more antidepressants?	Clinical data
Seven	**The underlying personality structure of depressed inpatients and the association between personality and TRD** **RQ6:** What is the underlying personality structure of depressed inpatients and is there an association between personality and TRD?	Clinical data
Eight	**Conclusion**	N/A

Chapter Two

The failure to define: a systematic review of the conceptualisation of treatment-resistant depression

2.1 Introduction

The objective of this chapter was to determine how TRD is currently conceptualised in the medical scientific literature by systematically reviewing the definitions employed and operationalised in randomised controlled trials (RCTs) of treatments administered for TRD. Treatment-resistant depression (TRD) has been acknowledged in the medical scientific literature since the 1970s as non-response to treatments known to be effective for depression. Despite major treatment advances, refractory depression has continued to be a significant clinical problem. The conceptualisation of TRD and how to define it in clinical practice has remained ambiguous and highly subjective.

RQ1. How TRD is identified and conceptualised in medical scientific literature.

A systematic review of the definitional concepts surrounding TRD was conducted to address the first research question. Randomised controlled trials (RCTs) of treatments for TRD were sourced using the methodology described by *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2008). In order to assess TRD in subsequent chapters of the thesis is was imperative to examine how TRD is currently conceptualised in medical scientific literature.

2.2 Background

The conceptualisation of depression has an extensive history, beginning with the writings of Ancient Greek and Egyptian physicians and philosophers such as Ebers Papyrus (1550 BC), Hippocrates (460-377 BC) and Aristotle (384-322 BC) and continuing into the twenty-first century with the development of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2010; Horwitz & Wakefield, 2007). The phenomenon of non-response to treatment known to be effective for depression has been acknowledged since the mid to late 1970s as ‘treatment refractory depression’ or, more commonly, as ‘treatment-resistant depression’ (TRD). Refractory or resistant depression has continued to be a significant clinical problem and remains a major contributor to the high rate of disability and global disease burden posed by major depression (Greden, 2001; Fekadu, Wooderson, Markopoulo,

Donaldson, Papadopoulos, & Cleare, 2009b). It is estimated that between 60% and 70% of individuals with a Major Depressive illness do not achieve complete remission from their symptoms (Horwitz & Wakefield, 2007). The exact prevalence of TRD is currently disputed due to ambiguity surrounding definitions of the phenomenon and because the prevalence rate varies according to the degree of treatment resistance that is being reported.

The body of research on TRD has continued to expand over the past 40 years. However, the conceptualisation of TRD and how to define it has remained inconsistent and subjective (Malhi, Parker, Crawford, Wilhelm, & Mitchell, 2005). Presently, the conceptualisation of TRD and its operationalisation in research and clinical practice is consensus driven rather than data driven (Berlim & Turecki, 2007a). This is because much about TRD is unknown and our ability to empirically test definitions is limited by heterogeneous research methodology and inconsistent findings (Malhi, Parker, Crawford, Wilhelm, & Mitchell, 2005). This has delayed the translation of research findings into clinical practice and has impeded the development of new treatment strategies aimed at improving the outcomes of patients who are resistant to treatment.

Earlier systematic reviews investigating the definitional concepts surrounding TRD noted that depression is considered resistant when an individual fails to achieve a significant clinical improvement after receiving two antidepressant trials (Berlim & Turecki, 2007a; Berlim & Turecki, 2007b). The failure of two antidepressants is currently the most commonly used definition in medical scientific literature but has been criticised as oversimplifying the concept of TRD (Rush, Thase, & Dube, 2003). As a result, several staging models have been developed in order to stage individuals on a continuum of treatment resistance (Fekadu, Wooderson, Markopoulo, Donaldson, Papadopoulos, & Cleare, 2009b; Fava, 2003; Souery, et al., 1999; Thase & Rush, 1997; Oquendo, et al., 2003; Sackeim, Prudic, Devanand, Decina, Kerr, & Malitz, 1990). However, these models have not yet been appropriately validated and not one has been adopted for widespread use by researchers and clinicians. All available models appear to stage TRD arbitrarily without an empirical rationale for their particular staging method. This approach is explained by Trivedi et al. (2006), who admit that models are based on algorithms of experience, expertise and anecdotal impressions rather than empirical data because data simply do not exist and much about TRD is still unknown.

Models and definitions of TRD are also limited by the infrequent use of measurement-based care (Matthew, 2008) and the incorporation of terms such as, ‘adequate’, ‘resistance’, ‘response’ and ‘failure’. The inconsistencies and controversies surrounding the conceptualisation of TRD also extend to these terms. How to define an adequate trial, sufficient treatment response and resistance to treatment is also debated and varies widely from study to study (see *1.9.2 The Six R’s of*

Treatment Outcomes). Response to treatment was once considered satisfactory if there was a reduction in baseline symptomatology as determined by a clinician-rated scale of depressive symptomatology - usually a 50% reduction of symptom score was required (Rush, Thase, & Dube, 2003; Janicak & Dowd, 2009). However, reduction of baseline symptoms is no longer the aim of treatment. Instead, remission with no residual symptoms is considered the preferred goal (Rush, Thase, & Dube, 2003). Residual symptomatology in individuals with depression is a risk factor for recurrence and is associated with poorer outcomes (Rush, Thase, & Dube, 2003; Rush, et al., 2006). A recent systematic review of short-term and long-term outcomes of individuals with TRD confirmed that residual symptoms lead to a higher incidence of recurrence in the short term and to the persistence of symptoms and disability in the long term (Fekadu, Wooderson, Markopoulo, Donaldson, Papadopoulos, & Cleare, 2009b).

Another contentious construct which is frequently used in definitions of TRD is 'adequacy'. Adequacy refers to the duration of a treatment trial and the dose administered throughout the treatment trial. Many individuals with TRD have had varying degrees of treatment adequacy and this has resulted in heterogeneous samples and limited interpretability and generalisability of findings. The term 'failure' is used interchangeably with 'non-response' and in its broadest sense can be defined as an unsatisfactory response to adequate treatment. There are also many other constructs associated with the phenomenon of TRD which are not systematically or universally defined in a standardised way. Rush, Thase and Dube (2003) identified nine parameters that should be explicitly defined in studies of TRD (see Table 2.1). The infrequent use of measurement-based care and inconsistent recording of individuals' treatment histories limit the reporting of these nine parameters.

Table 2.1

Rush, Thase and Dube's (2003) essential parameters to define when designing trials for TRD

Define a satisfactory clinical response
Define treatment resistance
Document treatment resistance
Specify the degree of resistance
Define the clinical characteristics of the sample
Define salient clinical outcomes e.g. level of response
Address tactical issues e.g. duration of trial, dosing pattern
Define options for trial design e.g. switching, augmenting, discontinuation
Benchmark comparisons

Against this background we aim here to systematically review the conceptualisation of TRD in the medical scientific literature by extracting definitions of treatment resistance and related underlying constructs. In particular, I focus on Rush, Thase and Dube's (2003) parameters of clinical response, definitions of treatment resistance, documentation of treatment resistance, clinical characteristics of the sample and the degree of resistance.

2.2.1 Hypotheses

RQ1. How TRD is identified and conceptualised in medical scientific literature.

It is hypothesised that the majority of studies will not have systematically defined or recorded these parameters and it is expected that there will be major variability in the measurement and definitions employed to these constructs.

2.3 Methods

Studies of interest were identified following the Cochrane Library guidelines for systematic reviews of interventions (Higgins & Green, 2008). The Cochrane Library guidelines identify three main bibliographic databases to search for RCTs to include in systematic reviews: the Cochrane

Central Register of Controlled Trials (CENTRAL), the Medical Literature Analysis and Retrieval System (MEDLINE) and EMBASE. These three databases were searched following the search strategy outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2008). The original search was conducted on September 13, 2012 and included all published trials from the earliest available RCTs of treatments for TRD up until September 13, 2012. Keywords and strings used to search for trials were "treatment-resistant depression" or "treatment refractory depression" or "resistant near treatment" and "depression" or "refractory near treatment" and "depression" AND "randomized controlled trial" or "randomized" or "clinical trial" or "randomly" or "controlled clinical trial". Systematic reviews of RCTs of treatments for TRD (Berlim & Turecki, 2007b; Bschor & Baethge, 2010; Daban, Martinez-Aran, Cruz, & Vieta, 2008; Lam, Chan, Wilkins-Ho, & Yatham, 2008; McPherson, Cairns, Carlyle, Shapiro, Richardson, & Taylor, 2005; Stimpson, Agrawal, & Lewis, 2002; Thomas, Nandhra, & Jayaraman, 2010) were hand-searched to identify other RCTs that the primary search did not identify. In total 3268 articles were retrieved from bibliographic databases and review articles and exported to an Endnote X3 database.

On November 1, 2014 the search was repeated using the original search criteria to update the review to include RCTs published between September 14, 2012 and October 31, 2014. Employing the original search criteria and databases, 1052 articles were retrieved with a publication date between January 1, 2012 and October 31, 2014. Out of the 1052 articles, 287 were published during January 1, 2012 and September 13, 2012 and were included in the original search. Almost 200 duplicates (N = 189) were detected and deleted. At the title level, 537 articles were excluded during the updated search. In total, 39 RCTs were examined at the full-text level with 22 RCTs meeting the inclusion criteria. These 22 RCTs were added to the 125 RCTs retrieved during the original search to reach the grand total of 147 RCTs included in this review. Figure 2.1 displays the process of identifying RCTs for the current systematic review.

Articles from the original and updated search were screened at the abstract and/or title level for potential inclusion into the systematic review. Inclusion criteria were as follows: (1) randomised control trial of treatments for TRD; (2) enrolled patients were considered resistant/non-responsive to treatment; (3) articles were peer reviewed; (4) published in English; and (5) enrolled patients 18 years and over. Using these criteria, 257 articles were assessed at the full text level for inclusion in the systematic review, with 147 articles meeting all inclusion criteria. Articles were excluded after examining full-text (N = 110) because they were either not randomised controlled trials (RCTs), were conference presentations rather than journal articles, were analyses of secondary data already published, were outcome studies rather than treatment trials, were published study protocols for

RCTs, were focused on treatments for medical illnesses rather than depression or were duplicates of studies already included.

For each of the 147 articles identified for this review the following information was retrieved from the full text: (1) sample size; (2) treatment strategy trialled; (3) terminology used to describe resistance; (4) definition of resistance/refractoriness; (5) justification of definition; (6) diagnostic tool used; (7) psychiatric exclusion criteria; (8) baseline symptomatology cut-off; (9) mean number of previous antidepressant trials; (10) assessment of response to previous antidepressant trials; (11) dose of previous antidepressant trials; (12) duration of previous antidepressant trials; (13) whether compliance of previous antidepressant trials were measured; (14) whether electroconvulsive therapy (ECT) was previously used and whether its response was measured. This information was retrieved from all articles using a systematic form. A summary of the extracted data can be viewed in Appendix 2. Data were analysed using Stata 12.

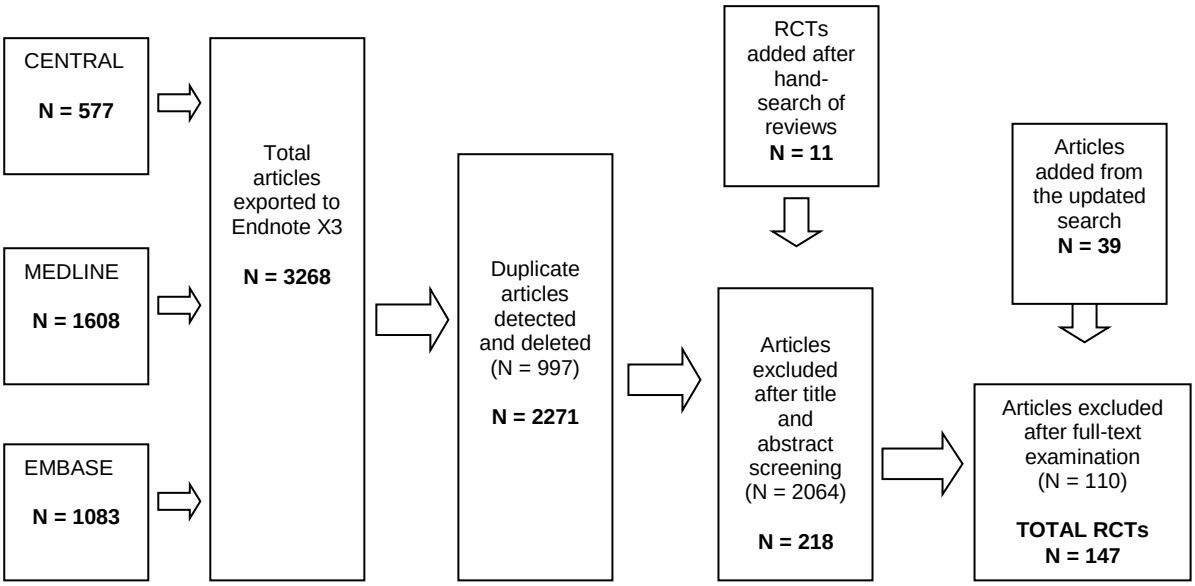


Figure 2.1. The process of identifying RCTs for the current systematic review

2.4 Results

2.4.1 Study characteristics. The earliest retrieved RCT included in the current review was published in 1974. However, the majority of the RCTs reviewed were published between 2000 and 2014 (N = 117; 79.6%). The mean sample size of the RCTs was 78.7 (SD = 110.6) and studies ranged in size from 5 to 605 participants. The most commonly trialled treatment strategies were drug augmentation treatments (N = 52; 35.4%) followed by transcranial magnetic stimulation (TMS) (N = 45; 30.6%) and antidepressant monotherapy (N = 14; 9.5%). The remaining studies

were RCTs of other treatments, such as ECT, ketamine infusions, physical exercise, combination strategies, vagus nerve stimulation, N-methyl-D-aspartate, tumor necrosis factor infusions, transcranial direct current stimulation, psychotherapy and magnetic seizure therapy (N = 36; 24.5%). More than half of the studies published in the 1990s (N = 23) were studies of augmentation strategies (N = 12; 52.2%). In the following decade (2000s; N = 72), drug augmentation strategies were less common (N = 25; 34.7%) and were superseded by TMS studies (N = 29; 40.2%) as the most common treatment strategy for TRD. In the past four years (N = 46; 2010 to 2014), ketamine infusions (N = 5; 10.9%) were introduced as treatments for TRD alongside more common treatments such as drug augmentation strategies (N = 13; 28.3%) and TMS (N = 13; 28.3%).

2.4.2 Terminology. The most frequently used term was "treatment-resistant depression", with most studies using the accompanying acronym "TRD" to describe the phenomenon of non-response to treatment (N = 73; 49.7%). The earliest appearance of the acronym TRD was in an RCT published in 1996. Prior to 1996 (N = 14), studies were more likely to use the term "resistant" (N = 6; 42.9%) or "refractory" (N = 4; 28.6%) to describe the non-response to treatment in individuals with depression. The term "treatment-resistant depression" and its accompanying acronym "TRD" has become common usage in recent years with over half the studies published between 2002 and 2014 (N = 109) using the term (N = 65; 59.6%). In addition to "TRD", eleven other terms were used to identify treatment resistance such as "medication resistant", "antidepressant non-responders" and "treatment refractory". Some RCTs specifically identified the type of treatment resistance in their terminology such as "SSRI-resistant" and "resistant to TCA" (N = 14; 9.5%). Alternatively, some RCTs were less specific and used ambiguous terminology to identify the type of treatment resistance by reporting participants who had "failed to respond" (N = 1; 0.7%) or had had an "inadequate response" to treatment (N = 1; 0.7%).

2.4.3 Definitions. Ten RCTs (6.8%) did not report how they defined treatment resistance. Table 2.2 displays the various definitions employed by RCTs in the current review. The most common definition reported was the failure of two or more antidepressants (N = 58; 39.5%) followed by the failure of one or more antidepressant (N = 42; 28.6%). The majority of studies (N = 112; 76.2%) used the definitions in Table 2.2 with various additional specifications of resistance. Some studies used two or more specifications such as, treatment failure within the "current episode and including an SSRI trial". The most frequent specification added to definitions of TRD is within the "current episode" (N = 29; 25.9%) and of "different classes of antidepressants" (N = 21; 18.8%).

Table 2.2

Definitions employed by RCTs in the current review

Definition	N (%)
Failure of two or more antidepressants	58 (39.5)
Failure of one or more antidepressant	42 (28.6)
Failure of only one antidepressant	10 (6.8)
No definition reported	10 (6.8)
Failure of two antidepressants	7 (4.8)
Non-response to antidepressants/treatment regimes/ multiple medications/ psychosocial and/or pharmacological interventions	6 (4.1)
Treatment resistance as per the Thase and Rush Model (1997)	4 (2.7)
Failure of three or more antidepressants	3 (2.0)
Failure of two different antidepressants or one antidepressant with lithium augmentation	1 (0.7)
Documented history of current episode antidepressant failure and a prospective failure of Fluoxetine	1 (0.7)
Treatment failure after one or more SSRIs in the current episode or failure after at least two classes of antidepressants in the current episode	1 (0.7)
A score above three on the Antidepressant Treatment History Form (ATHF)	1 (0.7)
A score above two on the Massachusetts General Hospital Staging Model (MGHS)	1 (0.7)
Failure of four or more antidepressants	1 (0.7)
Failure of three antidepressants in the previous six months	1 (0.7)
Total	147 (100)

2.4.4 Staging models of TRD. The majority of studies did not stage treatment resistance using the available staging models of TRD (N = 115; 78.2%). The Antidepressant Treatment History Form (ATHF) was used by 29 studies (19.7%) to assess the duration and dosage of previous trials. The Thase and Rush Staging Model (Thase & Rush, 1997) was utilised by 24 studies to justify their chosen definition of TRD (N = 24; 16.3%). The Massachusetts General Hospital Staging Model (MGHS) (Fava, 2003a) (N = 2; 1.4%) and the Maudsley Model (Fekadu et al., 2009a) (N = 1; 0.7%) were used by a small number of studies to define TRD. No studies that we identified had employed the European Staging Model (Souery, et al., 1999) to stage the level of treatment resistance in their study populations.

2.4.5 Inclusion criteria. The majority of studies reported the diagnostic criteria required by participants (N = 144; 98.0%). As expected, the most frequently required diagnosis was unipolar depression (N = 134; 91.2%) and the most frequently used set of diagnostic criteria were those for DSM-IV Major Depressive Disorder (MDD) or Major Depressive Episode (MDE). Table 2.3 lists the diagnostic systems used by RCTs to determine study inclusion. Some RCTs used more than one set of diagnostic criteria from Table 2.3 to confirm a diagnosis before entering participants into their trials (N = 3; 2.0%). Three studies were less specific on the diagnostic system used and reported "unipolar depression" (N = 1; 0.7%), "depression as confirmed by consensus of opinion" (N = 1; 0.7%) and "diagnostic criteria for use in psychiatric research" to diagnose "unipolar depression or depression secondary to anxiety or a character disorder" (N = 1; 0.7%). Thirteen RCTs (8.8%) included individuals with a diagnosis of Bipolar Affective Disorder.

The vast majority of studies (N = 116; 78.9%) required a minimum level of depressive symptom severity. The most common dimensional cut-off was having a score equal to or greater than 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D) (range ≥ 13 to ≥ 25) (N = 17; 11.6%). The HAM-D (either the 17-item, 21-item or 24-item scale) was the most frequently used rating scale (N = 73; 49.7%) with a minimum cut-off of 12 and a maximum cut-off of 26 used in various studies. Other rating scales included the Montgomery-Asberg Depression Rating Scale (MADRS) (N = 19; 12.9%), the Beck Depression Inventory (BDI-II) (N = 3; 2.0%), the Inventory of Depressive Symptomatology (IDS-C) (N = 4; 2.7%), the Quick Inventory of Depressive Symptomatology (QIDS) (N = 2; 1.4%), the Structured Interview Guide for the Hamilton Rating Scale for Depression – Seasonal Affective Disorder version (SIGH-SAD) (N = 1; 0.7%) and the Clinical Global Impression Scale (CGI) (N = 1; 0.7%). Twelve studies (8.2%) used two rating scales to confirm participants' eligibility for enrolment. Two studies described the severity of

depression required using the following descriptors “moderate to severe intensity” (N = 1; 0.7%) and “exhibition of primary depressive features” (N = 1; 0.7%).

Table 2.3

Diagnostic systems used determine inclusion into studies

Diagnostic Criteria	N (%)
DSM-IV[1]	119 (81.0)
DSM-III[2]	18 (12.2)
10th revision of the International Classification of Diseases (ICD-10)[3]	6 (4.1)
Feighner criteria[4]	1 (0.7)

[1]American Psychiatric Association, 2000; [2]American Psychiatric Association, 1980; [3]World Health Organisation, 1992; [4]Feighner et al., 1972;

2.4.6 Psychiatric exclusion criteria. Twenty five studies (N= 17.0%) did not report any psychiatric exclusion criteria. The remaining studies nominated the presence of one or more co-morbid psychiatric disorders that would lead to potential participants being excluded. Figure 2.2 depicts the proportion of studies which excluded a particular co-morbid psychiatric disorder. The most commonly excluded co-morbid disorders were substance abuse or dependence (N = 74; 50.3%), psychotic features or disorders (N = 60; 40.8%) and a bipolar affective disorder (N = 50; 34.0%). Indivdiuals who posed a suicide risk or suicidal ideation were excluded from 45 studies (30.6%).

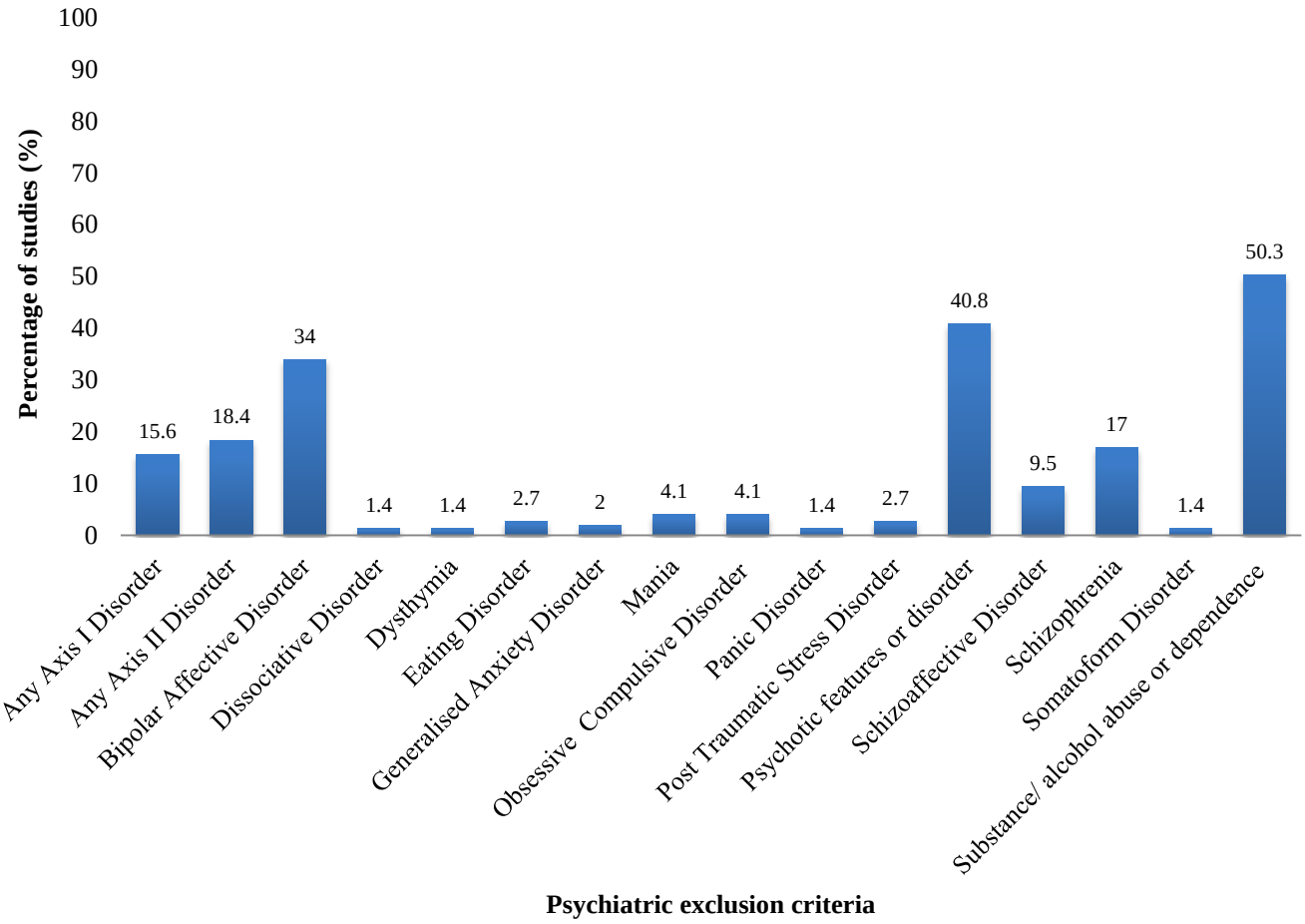


Figure 2.2. Co-morbid psychiatric conditions excluded from RCTs of treatments for TRD

2.4.7 Treatment history. Fifty-one studies (34.7%) reported the mean number of previous antidepressants trialled by the participants. On average, participants in these 51 studies had failed 5.3 (SD 3.1) antidepressant trials, with the mean number of previous trials ranging from 1.7 to 18.2 trials. Forty-nine studies (33.3%) assessed participants' adherence to previous treatment. Adherence was assessed either by self-report, monitoring antidepressant blood levels, counting the number of medication tablets or capsules returned or by the use of the Morisky Scale (Morisky, Ang, Krousel-Wood, & Ward, 2008). The Morisky Scale is an 8-item self-reported medication adherence scale developed to assess barriers to poor medication adherence (Morisky, Ang, Krousel-Wood, & Ward, 2008).

Participants' responses to previous antidepressant trials were not assessed in over half of the studies (N = 85; 57.8%). Of the studies that did assess participants' previous responses to treatment, 31 studies (21.1%) used known treatment assessment tools such as the Antidepressant Treatment History Form (ATHF) (Sackeim, Prudic, Devanand, Decina, Kerr, & Malitz, 1990; Oquendo, et al.,

2003), the Harvard Antidepressant History Form (HATH) (Nierenberg, Keck, Samson, Rothschild, & Shatzberg, 1991), Michigan Adequacy of Treatment Scale (MATS) (Grunhaus & Remen, 1993), The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) (Chandler et al., 2010), Treatment Response to Antidepressant Questionnaire (TRAQ) (Posternak & Zimmerman, 2003), and the Antidepressant Resistance Rating (ARR) scale (Prudic, et al., 1996; Sackeim, 2001). Sixteen studies (10.9%) used reduction in symptom severity to measure response to previous treatment. Previous treatment response was assessed by chart audit, patient recall and clinician judgment in eight RCTs (5.4%). Four studies (2.7%) assessed response to treatment by incorporating a prospective antidepressant trial and including only individuals who were non-responsive in that particular trial into the RCT. The remaining three studies (2.0%) outlined response to previous treatment in less detail, using descriptors such as "remained symptomatic", "still met criteria for a MDE" and "non-remission".

The assessment and definition of adequate treatment trials, in terms of the dose and duration of the trials, varied among the studies. Thirty-six studies (24.5%) did not report the dose of previous medication trials when assessing participants' previous responses to treatment. A substantial minority of studies (N = 63; 42.9%) reported that the doses used in previous medication trials were "adequate", of "standard effective dose", "therapeutic", "stable" or were of "maximum tolerated dose". Models and guidelines such as the Thase and Rush Staging Model (Thase & Rush, 1997), the ATHF (Sackeim, Prudic, Devanand, Decina, Kerr, & Malitz, 1990; Oquendo, et al., 2003) and the therapeutic guidelines approved by the Food and Drug Administration (US Food and Drug Administration, 2013) were used by some studies (N = 28; 19.0%) to justify their reported required dose of previous treatment.

Table 2.4

Durations of previous antidepressant trials

Duration of previous antidepressant trials	N (%)
At least 6 weeks or more	34 (23.1)
At least 4 weeks or more	26 (17.7)
At least 8 weeks or more	9 (6.1)
6 weeks	8 (5.4)
8 weeks	3 (2.0)
4 weeks	3 (2.0)
Greater than 4 weeks	1 (0.7)
Greater than 3 weeks	1 (0.7)
5 weeks of treatment	1 (0.7)
At least 3 months or more	1 (0.7)
At least 6 to 8 months	1 (0.7)

The duration of previous treatment trials was documented in 119 studies (81%). Table 2.4 displays the various durations of previous antidepressant trials required by participants in the RCTs. The ATHF (N = 21; 14.3%), MGHS (N = 1; 0.7%) and the APA guidelines (N = 1; 0.7%) were used by some studies to define the duration of previous antidepressant trials. Other studies reported the duration of antidepressant trials to be "adequate" (N = 7; 4.8%) or required participants to self-report previous trial durations (N = 1; 0.7%).

Sixty-one studies (41.5%) assessed whether their participants had received ECT. Twenty-five (41.0%) of these 61 studies assessed previous ECT treatment in order to exclude individuals who had received the treatment rather than to measure response to previous treatment.

2.5 Discussion

As expected, I found that the phenomenon of TRD has been inconsistently measured, with major variability in the definitions of TRD, reporting of previous treatment history and response. As a direct consequence of this high level of variability, it is unlikely that the studies in this review are measuring the same level of treatment resistance. Major heterogeneity in research methodology and varying levels of treatment resistance between patients indicate that it is more likely that these studies are reporting various stages of treatment non-response rather than the construct of TRD. The interchangeable use of the terms 'non-response' and 'TRD' is reducing the interpretability and generalisability of TRD. The term TRD should only be referenced in RCTs that include individuals who have failed to remit completely from their symptoms and still meet diagnostic criteria despite adequate treatment. The term non-response should be used to refer to individuals who have not experienced a reduction of symptom severity despite adequate treatment.

Variability was also found in the inclusion/exclusion criteria set by each study in the review. Historically, TRD has been associated with unipolar depression. More recently studies have been including individuals with bipolar disorder if the individual is in a depressed phase. It is proposed that the terms Treatment-Resistant Affective Disorders (TRAD; if both unipolar and bipolar patients are included) and Treatment-Resistant Bipolar (TRB; bipolar patients only) be used rather than TRD when including individuals with Bipolar Affective Disorders in clinical trials of treatment resistance. Rush, Thase and Dube (2003) noted that excluding most co-morbid disorders would improve the homogeneity of the studies but reduce the generalisabilty of the findings in clinical populations. Co-morbidity is unavoidable in RCTs of TRD due to the widespread use of convenience samples and the presumed high level of co-morbidity in TRD samples. Individuals may be pseudo-resistant to treatment because they have been misdiagnosed and consequently have been treated inappropriately. Therefore it is imperative to screen for co-morbidity and misdiagnosis before including individuals into RCTs of treatments for TRD. A greater focus on the impact of co-morbidity on TRD and a more standardised set of inclusion and exclusion criteria are required.

Despite the development of five staging models of TRD they have been rarely used to define or stage TRD. The staging models have been criticised as being too constrained and not measuring the major variability in TRD samples (Parker, Malhi, Crawford, & Thase, 2005). Instead of staging TRD using the available models, the most commonly used definition of TRD was the failure of two or more antidepressants. Studies that defined TRD as the failure of two or more antidepressants applied varying specifications to this superficially straightforward definition, making their findings difficult to compare between studies and difficult to generalise to all those patients who do not respond to treatment.

To some, the definition of the failure of two antidepressants as a proxy for TRD is too broad (Janicak & Dowd, 2009). Findings from the Sequential Treatment Alternatives to Relieve Depression (STAR*D) study support the belief that the failure of two antidepressant trials is not always indicative of TRD. Over a seven-year period the STAR*D study recruited 2876 outpatients from 41 clinical sites in the United States and tested four levels of treatment interventions (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). The cumulative remission rate for individuals who participated in Step 1 (a three month trial of citalopram) and Step 2 (a three month switch to another antidepressant or augmentation) of the STAR*D study was 58.7% (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Steps 3 (a three month switch to another antidepressant or augmentation) and 4 (a three month switch to another antidepressant) only added an additional 9% of remitted patients, resulting in a cumulative remission rate of 67.7%. Despite the diminution in remission rates across the steps, the difference between Step 2 and Step 4 cumulative remission rates indicate that after Step 2, when further strategies are trialled, individuals continue to remit (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). See Table 1.4 for more information on the STAR*D study design.

The STAR*D study results demonstrate that the failure of two antidepressants is perhaps more indicative of a failure to respond rather than a failure to remit as individuals may respond to alternative treatment strategies and to future treatment. This is also supported by the current review which found individuals on average had failed 5.3 antidepressant trials before entering the RCTs. However, the use of two antidepressants as a definition for TRD in clinical trials is understandable given that lowering the recruitment threshold would increase the sample size available for inclusion and increase the chance that the intervention will work (Rush, Thase, & Dube, 2003).

Over half the studies reviewed did not report their participants' previous responses to treatment or the adequacy of that treatment. The assessment of participants' previous treatment responses and history is essential when classifying an individual as resistant or when conducting any study on TRD. This is because the classification of an individual with TRD is dependent on patients' past responses to treatment and the previous treatments trialled. This also becomes important when considering how to define and assess the adequacy of previous treatment and also how to include individuals with tachyphylaxis, that is, individuals who once responded to drug treatment but now do not. Individuals with TRD will inevitably have experienced varying degrees of treatment adequacy and the level of adequacy can depend on clinicians' and patients' persistence with long trial durations (greater than 4 weeks) and the maximisation of doses despite limited initial response or adverse effects. Researchers should be concerned with treatment adequacy and the lack of measurement-based care not only when recruiting TRD patients but also when recruiting patients with non-TRD depression. There has been a call for a paradigm shift in the way patients with

depression are currently treated with a move away from the current 'trial and error' approach to selecting treatments and a push to introduce a treatment decision support system incorporating measurement based care and treatment algorithms to select treatment strategies (Trivedi & Daly, 2007). If greater systematic treatment selection is implemented in clinical practice then consistency in research might follow.

I propose the following recommendations to systematise the study design of TRD and to help develop a more cohesive construct of treatment resistance. In particular, I highlight the need for RCTs to disclose the type of treatment resistance, confirm the diagnosis using a standardised approach, list co-morbid disorders, outline the level of resistance and note previous treatment history in the sample. The creation of a more systematic study design will result in more replicable findings and a clearer picture of TRD. Table 2.5 outlines future recommendations for RCTs of treatment resistance.

Currently, TRD is being used as a 'catchall' category of non-response and difficult-to-treat depression rather than a systematic nosological construct of treatment resistance (Malhi, Parker, Crawford, Wilhelm, & Mitchell, 2005). The DSM-5 has introduced Persistent Depressive Disorder to replace both Dysthymic Disorder and Major Depressive Disorder with "chronic" specifier. This addition has the potential to become the new 'catchall' diagnosis of difficult-to-treat depression and individuals resistant to or avoidant of treatment. Chronic depressive states have been associated with poorer response to treatment (Klein, Shankman, & Rose, 2006), more complex psychopathology (Gilmer, et al., 2005; Satyanarayana, Enns, Cox, & Sareen, 2009) and greater levels of disability (Gilmer, et al., 2005; Satyanarayana, Enns, Cox, & Sareen, 2009). TRD is also associated with greater disability and a more chronic course of depression (Dunner et al., 2006). The implication of the association between TRD and Persistent Depressive Disorder is yet to be seen. However, because Persistent Depressive Disorder has diagnostic criteria in the DSM-5 it is possible that this new diagnosis will supersede TRD as the label for treatment resistance and difficult-to-treat depression.

Table 2.5

Recommendations for clinical trials on treatment resistance

Recommendation	Details to report in RCTs
Specify type of treatment resistance	Identify study sample as either: o Treatment Resistant Depression (TRD) o Treatment Resistant Bipolar (TRB) o Treatment Resistant Affective Disorders (TRAD)
Confirm diagnosis	o State the inclusion diagnosis required e.g. Major Depressive Disorder o Report how the diagnosis was confirmed e.g. using the MINI/CIDI/SCID or consensus by two clinicians o Report participants excluded due to misdiagnosis o Report co-morbidity for each level of resistance
Outline level of resistance	o Include table that summarises the level of resistance of participants e.g. report the number of participants who have failed one antidepressant, two antidepressants, three antidepressants etc. OR reference model and report stages of resistance as per the particular model
Report treatment history	o Report response to ECT and other physical therapies o Define treatment adequacy and report the level of treatment adequacy in the sample
Findings	o Report results specific to level of resistance e.g. more effective in individuals who had failed only one antidepressant compared to individuals who have failed three antidepressants o Report on differences in results due to levels of co-morbidity or treatment adequacy e.g. if previous treatment was not adequate they were more likely to respond to the current treatment

No matter what the impact of the DSM-5 will have on the conceptualisation of TRD, a more definitive and standardised conceptualisation of treatment resistance needs to be developed.

Currently there has been failure to define the concept in a systematic and universal way. This has impeded research efforts and delayed the development of appropriate treatment strategies for these individuals. In particular, a panoptic model of TRD should be considered incorporating measurement-based care outcomes and other multidimensional facets of this phenomenon. More research using systematic study designs and well-defined samples is required to increase the interpretability of findings. Only then will it be possible to study TRD more effectively and improve the longer-term outcomes of individuals with resistant depression.

Chapter Three

Research Methodology A: Epidemiological Data

Note. Sections of this chapter have been published in Murphy & Byrne (2012). Prevalence and correlates of the proposed DSM-5 diagnosis of Chronic Depressive Disorder. *Journal of Affective Disorders.* 139. 172–180 (Appendix 4). Although Chronic Depressive Disorder was the preferred term in the draft DSM-5 criteria, this was changed to Persistent Depressive Disorder in the final published version of the DSM-5.

3.1 Introduction

This is the first of two methodology chapters and deals with secondary analyses of national population-level data on chronic depression. Following the systematic review of the concept of TRD (Chapter Two), the next step was to estimate the prevalence and further characterise TRD at the national population level. The 2007 NSMHWB appeared to provide the opportunity to do this. However, TRD as it is generally conceptualised, was not identifiable in the NSMHWB data set due to the limited treatment information collected in the survey. However, it was possible to investigate the prevalence and correlates of a closely related phenomenon, chronic or persistent depression. These findings are reported in Chapter Four. Using the 2007 NSMHWB it was possible to assess differences in health service utilisation and the characteristics of chronically depressed individuals who sought health services in tertiary care settings. Chronically depressed individuals in the community who seek tertiary level mental health services may overlap to some extent with patients with TRD found in inpatient settings. The purpose of this chapter is to detail the research methodology underpinning the 2007 NSMHWB.

3.2 The National Survey of Mental Health and Wellbeing (NSMHWB)

In 1992, the Commonwealth, State and Territory governments of Australia developed a National Mental Health Strategy which acknowledged the lack of epidemiological data on the prevalence of mental illness in community-residing Australians (Australian Bureau of Statistics, 2007). In order to meet this need, the then Commonwealth Department of Health and Family Services (HFS) commissioned the first NSMHWB. The survey was conducted in 1997 by the Australian Bureau of Statistics (ABS) and was comprised of an adult study, a child and adolescent study and a study of low prevalence psychotic disorders (Australian Bureau of Statistics, 2007). The 1997 NSMHWB assessed the prevalence of 12-month mental disorders, disability associated with these disorders and the health service utilisation of individuals with mental disorders (Australian Bureau of Statistics, 2007).

Ten years later, in 2007, the second NSMHWB was conducted by the ABS and was funded by the Australian Government Department of Health and Ageing (DoHA). Unlike the 1997 survey, the 2007 survey was designed to provide both lifetime and 12-month prevalence estimates of mental health disorders in community-residing Australians (Australian Bureau of Statistics, 2007). In addition, the 2007 NSMHWB collected information on the level of impairment and disability of mental disorders, demographic and socio-economic characteristics, physical conditions, health service utilisation and social networks (Australian Bureau of Statistics, 2007). A main focus of the survey was to provide internationally comparable prevalence estimates of mental disorders and to estimate the health service utilisation of community-residing Australians with mental disorders (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). These estimates help guide policy decisions and assess the adequacy of the mental health care system for community residing Australians.

3.3. Sample

Survey interviews were conducted between August and December 2007 (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). In brief, urban and rural households from Australian states and territories were selected at random using a stratified, multistage, area sampling method with a response rate of approximately 60% (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). The initial sampling procedures used by the ABS resulted in 17,352 dwellings to approach for inclusion (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). A total of 2,547 dwellings were deemed ineligible (i.e. not occupied), resulting in 14,805 possible dwellings to be included in the survey. Of these 14,805 possible dwellings, one individual between the ages of 16 and 85 years from 8,841 households provided informed consent and completed the survey interview (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). There were 5,964 households that either refused to take partake in the survey (61%), did not complete the full survey (21%) or provided incomplete information (12%) (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). The final sample of 8,841 respondents represented an estimated population count of 16,015,000 community-residing Australians (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009).

Young people (16 to 24 years old) and older people (65 to 85 years old) were over-sampled to improve standard errors. The data were weighed according to the inverse probability of being selected in the survey (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). The weights were devised using 2006 census data and were benchmarked against household composition, age, gender, labour force status and educational attainment (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009).

3.4 Survey interview

Respondents were interviewed using the World Mental Health Survey Initiative version of the World Health Organization's Composite International Diagnostic Interview, version 3.0 (WMH-CIDI 3.0) (Kessler & Ustun, 2004). The WMH-CIDI has been used in at least 28 countries for epidemiological surveys and has been continually modified and updated since its inception in 1990. It is a fully-structured interview designed to collect information on a range of mental disorders, as well as information on risk factors, disease burden, patterns of co-morbidity and treatment of mental disorders (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). Select parts of the WMH-CIDI 3.0, which is based on international survey modules, were adapted for use with the Australian sample. In particular, some modules were removed to reduce the length of the interview and some language edits were made for an Australian setting (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). In addition, an Australian health service use and medication use module was added.

The WMH-CIDI 3.0 produces ICD-10 and DSM-IV diagnoses based on provided diagnostic algorithms. Three main diagnostic classes were assessed in the 2007 NSMHWB: 1) affective disorders - depression, dysthymia, bipolar affective disorder; 2) anxiety disorders - agoraphobia, social phobia, panic disorder, generalised anxiety disorder, obsessive compulsive disorder and post-traumatic stress disorder; and 3) substance use disorders - harmful use and dependence for alcohol, cannabis, sedatives, stimulants and opioids (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009).

3.5 Overview of main findings from the 2007 NSMHWB

Almost half of the Australian population met criteria for an anxiety, affective and/or substance use disorder during their lifetime (45.5%, 95% CI: 44.1-46.9%) (Australian Bureau of Statistics, 2007; Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). One in five community-residing individuals met criteria for a 12-month mental disorder (anxiety, affective and/or substance use disorder) (20%; 95% CI: 18.9 - 21%) (Australian Bureau of Statistics, 2007; Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). Anxiety disorders were the most common 12-month mental disorder (14.4%, 95% CI: 13.4-15.3%) followed by affective disorders (6.2%, 95% CI 5.5-6.9%) and substance use disorders (5.1%, 95% CI 4.5-5.8%) (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). Females were more likely to experience a 12 month mental disorder compared to males (22.3% 95% CI 21 – 23.6% and 17.6% 95% CI 15.7 – 19.5%, respectively) (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). The young adult cohort (16 to 24 years old) had the highest prevalence of 12-month mental disorders, with the

prevalence of 12-month mental disorders declining with age (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009).

In regards to severity, affective disorders were associated with the greatest severity with just over half of individuals with an affective disorder classified as severe (51%; 95% CI 42.6-59.5%) (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). One in five individuals with any 12-month mental disorder experienced one co-morbid mental disorder during the same 12-month period (21.9%, 95% CI 19.3-24.5%) (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). It was less common for individuals to experience all three disorder classes (anxiety, affective and/or substance use) during the same 12-month period (3.5%; 95% CI 2.3-4.7%) (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009).

One third of individuals diagnosed with a 12-month mental disorder reported that they had used health services for their mental health in the preceding 12-months (34.9%; 95% CI: 31.3-38.5%) (Australian Bureau of Statistics, 2007). Types of health services included general practitioner (GP; primary care physician) consultations, psychologist/psychiatrist consultations, hospital admissions and self-management strategies (e.g. support groups). Individuals with a 12-month affective disorder were the most likely to access health services and those with a substance use disorder were the least likely to access health services (58.6% 95% CI: 49.9-67.4% and 24.0% 95%CI 16.5-31.4% respectively) (Australian Bureau of Statistics, 2007). Women were more likely than men to visit a GP for their 12-month mental disorder (41% vs. 28% respectively) (Australian Bureau of Statistics, 2007). Those who had two or more mental disorders in the past 12-month were twice as likely to use health services when compared to those with only one 12-month mental disorder (52% vs. 23% respectively) (Australian Bureau of Statistics, 2007).

3.6 Sample selection for Chapter Four

Of the 8,841 individuals interviewed for the 2007 NSMHWB, 1,366 (15.1%; 95% CI: 14.1%–16.0%) were assigned a lifetime DSM-IV diagnosis of either MDD or Dysthymic Disorder, or both. There were 229 individuals who met criteria for both a lifetime diagnosis of MDD and a lifetime diagnosis of Dysthymic Disorder, and 25 individuals who had only a diagnosis of Dysthymic Disorder. The remaining 1,112 individuals in the depressed sub-sample had a lifetime diagnosis of MDD, with no Dysthymic Disorder. It should be noted that one individual with MDD was excluded from the analysis due to missing data on episode duration and persistence variables. Individuals with a history of Bipolar Disorder were not excluded from the study.

3.7 Classification of chronic depression cases

All individuals with a lifetime diagnosis of Dysthymic Disorder (N = 254) were classified as having chronic depression. To identify which of the 1,111 individuals with MDD but no Dysthymic Disorder had a chronic course of depression, the duration or persistence of symptoms was used as the indicator of chronicity. The WMH-CIDI 3.0 assessed persistence of MDD by asking individuals to recall their worst episode of being "sad or discouraged or uninterested" when they also had "the largest number of other problems". The "largest number of other problems" referred to the subjects' previously reported depressive symptoms, including problems with appetite, sleep and concentration. The diagnostic interview also assessed how old the person was at the start of the episode and the duration of the episode. For the purposes of this analysis, and in line with the duration criterion for the DSM-5 Persistent Depressive Disorder, individuals who had a lifetime diagnosis of MDD and who had a persistence of two years or more were defined as chronic (N = 144) and those with a persistence of less than two years were defined as non-chronic (N = 967). Using this approach, participants were divided into two groups, those with chronic depression (i.e., those with MDD and persistence equal to or greater than two years, and those with Dysthymic Disorder; N = 398; coded 1) and those with non-chronic depression (i.e., those with MDD and persistence less than two years; N = 967; coded 0) (see Figure 3.1).

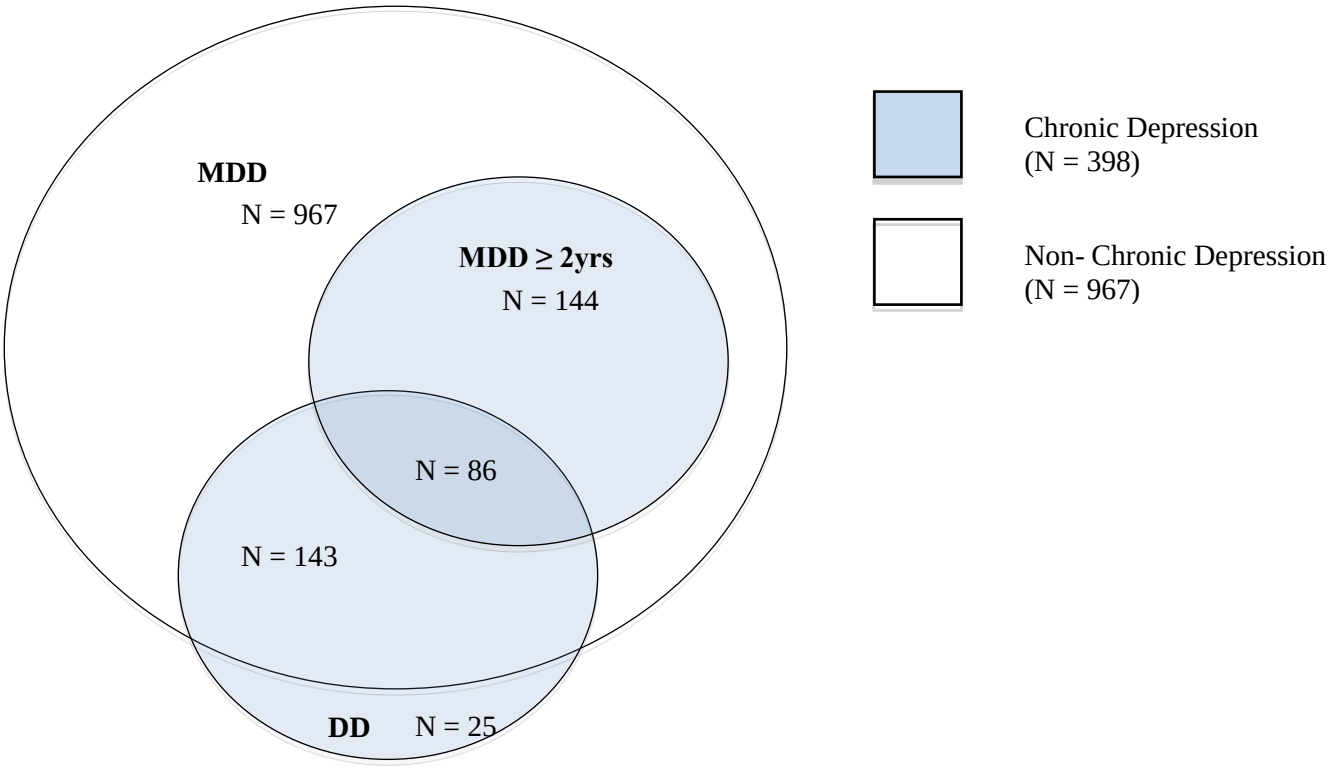


Figure 3.1. Venn diagram showing the overlap of individuals with a lifetime diagnosis of both Dysthymic Disorder (DD) and Major Depressive Disorder (MDD) with a chronic course of 2 years or more (data from the 2007 NSMHWB).

3.8 Ethical Considerations

The 2007 NSMHWB is available in the public domain and can be accessed by researchers with approval from the ABS. The data is confidentialised to protect respondents prior to being released by the ABS. Approval was granted by the ABS on the 11 December 2009 to use the 2007 NSMHWB Confidentialised Unit Record File (CURF) on CD-ROM for the purpose of the current study (see Appendix 3). The University of Queensland Medical Research Ethics Committee also approved the secondary data analysis of the 2007 NSMHWB for PhD research (ethics approval number: 20100000124) (see Appendix 3).

Chapter Four

Chronic depression in the Australian community

Note. Sections of this chapter have been published in Murphy & Byrne (2012). Prevalence and correlates of the proposed DSM-5 diagnosis of Chronic Depressive Disorder. *Journal of Affective Disorders.* 139. 172–180 (Appendix 4). Although Chronic Depressive Disorder was the preferred term in the draft DSM-5 criteria, this was changed to Persistent Depressive Disorder in the final published version of the DSM-5.

4.1 Introduction

This chapter examines chronic depression in community-residing individuals via secondary analysis of data from the 2007 NSMHWB. The primary aim of this chapter is to determine the prevalence of chronic depression in community-residing individuals and examine what factors are associated with chronic depression. Investigating chronic depression in community-residing individuals provides the opportunity to assess the illness burden posed by depression and examine the level of support for the established view that depression can be chronic, recurrent, and, at times, unresponsive to treatment. As such, data from the national survey may provide some insight into the phenomenon of TRD.

Chronic depression, defined broadly as a depressive illness with duration greater than two years may conceptually overlap with TRD. However, the association between chronic depression and TRD is difficult to untangle. In Western societies in which citizens have good or reasonably good access to primary health care, chronic depression is almost always associated with poorer response to treatment and TRD is often reported to be chronic and long-standing (Fekadu, Wooderson, Markopoulo, Donaldson, Papadopoulos, & Cleare, 2009b; Keller, McCullough, Klein, Arnow, Dunner, & Gelenberg, 2000; Vergunst, et al., 2013; Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). However, there are caveats to this circularity. Untreated chronic depression cannot be considered treatment resistant just as resistance to treatment during a first episode of depression cannot be labelled chronic. Thus, while there is a degree of conceptual overlap between chronic and TRD, they are not completely interchangeable concepts.

Therefore, an additional aim of this chapter is to assess the health service utilisation of chronically depressed individuals in order to assess how many community-residing individuals with chronic depression are untreated and to investigate what factors are associated with differing health service utilisation in individuals with chronic depression. The types of service utilisation compared are untreated (no service utilisation), outpatient treatment only (primary care) and both inpatient and outpatient treatment (tertiary care). The primary purpose of assessing these three types of

service utilisation is to determine whether individuals who seek tertiary care are more chronic and complex than individuals who are untreated or who have received primary care only. Individuals with chronic depression may be found in tertiary care settings because they exhibit treatment resistance or because they are generally more help-seeking than others. The research questions addressed in this chapter are:

RQ2. What is the prevalence of chronic depression in community-residing individuals and what factors are associated with chronic depression?

RQ3. Are community-residing individuals with chronic depression who utilise higher level health services (i.e. those seen in tertiary care settings) more likely to exhibit characteristics associated with TRD (such as displaying a more chronic and complex presentation) than those with chronic depression who remain untreated or who use lower levels of health services (i.e. those seen in primary and secondary care settings)?

These research questions are addressed utilising the 2007 NSMHW. Chronic depression is identified and modelled on the DSM-5 diagnosis of Persistent Depressive Disorder which is broadly defined as a "depressed mood for most of the day, for more days than not, for at least two years" (DSM-5, 2014). Chronic depression is compared to non-chronic depression on socio-demographic and clinical features. Particular attention is given to the differences in the presence and onset of co-morbid psychiatric conditions between chronic and non-chronic depression. Research Question 3 is addressed by identifying the health service utilisation of individuals in the Australian community with chronic depression. The degree of health service utilisation in the sample is assessed and individuals with chronic depression who never received treatment, received primary care treatment only or received tertiary care treatment are compared. The primary purpose of Research Question 3 is to investigate whether individuals with chronic depression who utilise higher-level health services are more complex and exhibit potential treatment resistance.

4.2 Background

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) put forward criteria for a new diagnosis called, Persistent Depressive Disorder (American Psychiatric Association, 2010). This new diagnosis encompasses DSM-IV Dysthymic Disorder and those cases of Major Depressive Disorder (MDD) with chronic specification (American Psychiatric Association, 2000). Persistent Depressive Disorder was proposed for DSM-5 in response to research findings highlighting the homogeneous nature of the various types of chronic depressive

states (American Psychiatric Association, 2010). In particular, it was argued that Dysthymic Disorder, MDD with chronic specification, and so-called double depression (combined MDD and Dysthymic Disorder) could not be satisfactorily differentiated, either clinically or etiologically (Klein, 2008; McCullough, et al., 2003; Rhebergen, et al., 2009). The diagnostic criteria for DSM-5 Persistent Depressive Disorder are summarised in Table 4.1.

Although Dysthymic Disorder, MDD with chronic specification, and double depression did not vary enough from each other to warrant their continuation as distinct disorders, they did appear to vary significantly from non-chronic MDD (Klein, 2008; Klein, Shankman, & Rose, 2006; McCullough, et al., 2003; Rhebergen, et al., 2009). In comparison with non-chronic MDD, the chronic depression sub-types have different disease courses, lower response rates to treatment, higher rates of family history and more psychiatric co-morbidity (Alnaes & Torgersen, 1997; Angst, Gamma, Rossler, Ajdacic, & Klein, 2009; Klein, Shankman, & Rose, 2006; McCullough, et al., 2003; Mondimore, et al., 2007). The distinction between chronic and non-chronic depression is stable over time with chronic individuals being fourteen times more likely than non-chronic individuals to have a chronic presentation ten years later (Klein, Shankman, & Rose, 2006). It was argued that the distinction between chronic and non-chronic depression may be more clinically and etiologically relevant than any of the distinctions between the various sub-types and manifestations of chronic depression as they were represented in DSM-IV (Klein, Shankman, & Rose, 2006; McCullough, et al., 2003; Mondimore, et al., 2007).

Table 4.1

Comparison of diagnostic criteria for DSM-IV Dysthymic Disorder and DSM-5 Persistent Depressive Disorder.

DSM-5 Persistent Depressive Disorder	DSM-IV Dysthymic Disorder
A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years.	A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years.
B. Presence, while depressed, of two (or more) of the following: 1. Poor appetite or overeating 2. Insomnia or hypersomnia 3. Low energy or fatigue 4. Low self esteem 5. Poor concentration or difficulty making decisions 6. Feelings of hopelessness	B. Presence, while depressed, of two (or more) of the following: 1. Poor appetite or overeating 2. Insomnia or hypersomnia 3. Low energy or fatigue 4. Low self esteem 5. Poor concentration or difficulty making decisions 6. Feelings of hopelessness
C. During the 2-year period of the disturbance, the person has never been without the symptoms in Criteria A and B for more than 2 months at a time.	C. During the 2-year period of the disturbance, the person has never been without the symptoms in Criteria A and B for more than2 months at a time.
D. The disturbance does not occur exclusively during the course of a chronic Psychotic Disorder, such as Schizophrenia or Delusional Disorder.	D. No Major Depressive Episode has been present during the first 2 years of the disturbance, i.e. the disturbance is not better accounted for by chronic Major Depressive Disorder, or Major Depressive Disorder, In Partial Remission.
G. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, medication) or general medical condition (e.g. hypothyroidism)	E. There has never been a Manic episode, a Mixed episode or a Hypomanic episode, and criteria have never been met for Cyclothymic Disorder.
H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	F. The disturbance does not occur exclusively during the course of a chronic Psychotic Disorder, such as Schizophrenia or Delusional G. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, medication) or general medical condition (e.g. hypothyroidism) Disorder. H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

As expected, chronic depressive disorders have been associated with a slower rate of improvement over time and a poorer response to treatment in comparison with non-chronic MDD (Klein, Shankman, & Rose, 2006). In addition, longer episode durations with fewer lifetime episodes (Gilmer, et al., 2005; Rush, Laux, Jarrett, Weissenburger, Feldman-Koffler, & Stone, 1995) and higher rates of suicidal ideation have been associated with chronic depression (Satyanarayana, Enns, Cox, & Sareen, 2009). Chronicity has also been linked to a wide range of factors, including the following: higher rates of family history of mood disorder (Mondimore, et al., 2007); early childhood trauma or adversity (Gopinath, Katon, Russo, & Ludman, 2007; Honkalampi, Hintikka, Haatainen, Koivumaa-Honkanen, Tanskanen, & Viinamaki, 2005; Wiersma, et al., 2009); a negative cognitive style (Riso, et al., 2003); higher rates of medical and psychiatric co-morbidity (Gilmer, et al., 2005; Satyanarayana, Enns, Cox, & Sareen, 2009; Viinamaki, et al., 2006); older age (Gilmer, et al., 2005; Rush, Laux, Jarrett, Weissenburger, Feldman-Koffler, & Stone, 1995); less education (Gilmer, et al., 2005); lower socioeconomic status (Gilmer, et al., 2005); lack of health insurance (Gilmer, et al., 2005); and a rural place of residence (Viinamaki, et al., 2006). Also associated with a more chronic course of depression are greater levels of disability (Ormel, Oldehinkel, Nolen, & Vollebergh, 2004; Satyanarayana, Enns, Cox, & Sareen, 2009), poor subjective health (Honkalampi, Hintikka, Haatainen, Koivumaa-Honkanen, Tanskanen, & Viinamaki, 2005), insufficient social support (Honkalampi, Hintikka, Haatainen, Koivumaa-Honkanen, Tanskanen, & Viinamaki, 2005) and lower self-efficacy (Gopinath, Katon, Russo, & Ludman, 2007). However, these latter factors might be consequences rather than causes of chronicity.

Much of what is known about the sociodemographic and clinical correlates of chronic depression has come from studies of ambulatory clinic populations. Very few population based community studies have investigated chronic depression, and as a consequence, available research findings might not generalise well to the population at large. One US community-based epidemiological study estimated that the prevalence of persistent depression in the general population is 3.4% (Young, Klap, Shoai, & Wells, 2008). A recent Canadian study, based on a national population-based survey, found that those with chronic depression represented 26.8% of all individuals with MDD and that chronicity was associated with higher rates of psychiatric and medical co-morbidity, greater disability, increased health service use and higher rates of suicidal ideation and attempts (Satyanarayana, Enns, Cox, & Sareen, 2009). The Netherlands Mental Health Survey and Incidence Study (NEMESIS), an earlier community-based study, estimated that 20% of those with depression had a more chronic course (Spijker, de Graaf, Bijl, Beekman, Ormel, & Nolen, 2002).

As the DSM-5 explicitly acknowledges the distinction between chronic and non-chronic depressive states and there is increased recognition of the magnitude of the public health burden associated with depression (Murray & Lopez, 1996), it is timely to explore the prevalence and correlates of chronic depression in the community. Accordingly, I investigate the prevalence and correlates of chronic depression in an Australian population-based sample of community-residing individuals.

4.3 Methods

The research methodology for the 2007 NSMHWB can be found in Chapter Three.

4.3.1 Putative correlates. Putative correlates, including age, gender, employment status, age of onset and number of depressive episodes, were assessed by the WMH-CIDI 3.0 interviewer and relied on participant recall. Suicidal ideation was measured with a dichotomous item asking whether the individual had ever thought about committing suicide during their worst "sad/ discouraged/uninterested" episode. Depression symptom severity was assessed by asking participants to rate the severity of their emotional distress on a four-point scale (mild/moderate/ severe/very severe) during their worst episode.

Current psychological distress was measured on the 10-item Kessler Psychological Distress Scale (K-10), with higher scores indicating higher levels of psychological distress (minimum score, 10; maximum score, 50) (Kessler, et al., 2002). Current disability was measured on the 12-item World Health Organization Disability Assessment Schedule (WHODAS II), with higher scores indicating higher levels of disability (minimum score, 0; maximum score, 100) (World Health Organization, 2001). Psychiatric co-morbidity was estimated by counting the total number of lifetime DSM-IV disorders detected by the WMH-CIDI 3.0 interview (minimum score, 1; maximum score, 11). Family history was measured by asking participants how many first-degree relatives they had with depression. Medical co-morbidity was estimated by counting the total number of chronic medical conditions reported by each participant (minimum score, 0; maximum score, 11). Traumatic load was estimated by counting the total number of lifetime traumatic events reported by each participant (minimums core, 0; maximum score, 29). The hopelessness and worthlessness measures were self-reported items of the K-10 (minimum score, 1= none of the time; maximum score, 5= all of the time).

4.3.2 Statistical analyses. Data analyses were conducted in Stata 11 (StataCorp LP, 2009) using survey data routines. Individualised person weights were used to allow population estimates to be calculated. Standard errors of prevalence estimates and confidence intervals around odds ratios were calculated on the basis of delete one jackknife replications using 60 replicate weights provided by the ABS. This approach was necessary because of the confidentialised nature of the

unit record data set. The prevalence estimates reported take into account the probability of being sampled and have been standardised to the projected 2007 age and sex distribution of the Australian population based on the 2006 population census (Australian Bureau of Statistics, 2007).

The lifetime prevalence of co-morbid disorders was estimated controlling for respondent age at time of interview. The temporal relationships between chronic and non-chronic depression and lifetime co-morbidity were investigated using retrospective age of onset reports, which were graphed using discrete-time survival analyses with person– year as the unit of analysis. The method of using person– year as the unit of analysis for survival analysis is described elsewhere (Nock, et al., 2009).

Putative factors associated with chronic depression that were identified in the research literature and factors found in bivariate analyses with $p<.01$ were included in a multivariable logistic regression model. Some variables were collapsed into fewer categories due to the presence of redundant categories or for ease of interpretation. In particular, symptom severity was dichotomised into non-severe and severe symptoms and number of episodes was dichotomised into either three or fewer episodes or four or more episodes. Descriptive statistics for the variables used in the multivariable model are presented in Table 4.2. Wald chi-square tests (χ^2) were used to test the significance of each coefficient in the final model. The Hosmer–Lemeshow test was used to assess the goodness-of-fit of the final model.

Chi-square tests and one-way between groups analysis of variances (ANOVA) were used to assess differences in socio-demographic and clinical features between three health service utilisation groups (primary care, tertiary care and untreated CD).

4.4 Results

4.4.1 Prevalence and socio-demographic correlates. Chronic depression (CD), which included 229 individuals with both a lifetime diagnosis of MDD and a lifetime diagnosis of Dysthymic Disorder, 25 individuals with only Dysthymic Disorder and 144 individuals with persistent/chronic MDD was present in 29.4% (95% CI: 25.6%–33.3%) of all individuals with a lifetime depressive disorder (MDD and/or Dysthymic Disorder). The population-weighted estimate of the lifetime prevalence of chronic depression in community residing persons was 4.6% (95% CI: 3.9–5.3%), with non-chronic depression (NCD) having an estimated lifetime prevalence of 10.4% (95% CI: 9.6–11.2%).

Socio-demographic and clinical comparisons between individuals with CD and NCD are summarised in Table 4.2. As expected in a sample of depressed individuals, females outnumbered males in both groups. In comparison with NCD individuals, those with CD were older and more likely to be unemployed.

Table 4.2

Sociodemographic and clinical features associated with chronic and non-chronic depression

	Non-Chronic (N = 967)	Chronic (N = 398)				
Feature	N (%) / Mean ± SD	N (%) / Mean ± SD	OR	95% CI	t	p
Age (years)	43.07 ± 15.84	47.24 ± 15.38	1.01	1.00 – 1.02	3.07 [a]	< .003
Gender						
Female	628 (64.94)	262 (65.83)				
Male	339 (35.06)	136 (34.17)	1.00	.72 – 1.39	.02	.982
Education						
Tertiary	409 (42.30)	130 (32.66)				
High school level	369 (38.16)	196 (49.25)	1.63	1.11 – 2.41	2.53	.014
Skilled vocation	189 (19.54)	72 (18.09)	1.28	.79 – 2.07	1.01	.315
Employment Status						
Employed	651 (67.32)	209 (52.51)				
Unemployed	316 (32.68)	189 (47.49)	2.09	1.44 – 3.03	3.97 [a]	< .001
Number of episodes						
Fewer no. of episodes (≤ 3) [b]	663 (69.86)	158 (43.05)				
Greater no. of episodes (> 3) [b]	286 (30.14)	209 (56.95)	3.24	2.17 – 4.85	5.84 [a]	< .001
Age of Onset (years)	29.37 ± 14.66	25.35 ± 14.43	.98	.96 - .99	-3.40 [a]	< .001
Symptom Severity						
Non-Severe symptoms	316 (32.68)	82 (20.60)				
Severe symptoms	651 (67.32)	316 (79.40)	1.79	1.16 – 2.76	2.67	.010
No. of Family Members with Depression	.41 ± .71	.62 ± .91	1.23	.97 – 1.55	1.75	.086
Suicidal ideation						
No	575 (59.46)	177 (44.58)				
Yes	392 (40.54)	220 (55.42)	1.69	1.11 – 2.58	2.49	.016
Previous suicide attempt(s)						
No	849 (87.80)	315 (79.35)				
Yes	118 (12.20)	82 (20.65)	1.78	1.14 – 2.76	2.61	.011
No of. co-morbid psychiatric disorders	2.62 ± 1.67	4.11 ± 2.18	1.48	1.34 – 1.63	8.17 [a]	< .001
No of. co-morbid medical conditions	2.17 ± 1.98	3.03 ± 2.50	1.18	1.09 – 1.27	4.47 [a]	< .001
Traumatic load	3.06 ± 2.77	4.13 ± 3.27	1.12	1.05 – 1.19	3.41 [a]	< .001
Current disability (WHODAS12)	12.57 ± 13.83	20.83 ± 18.83	1.03	1.02 – 1.04	6.50 [a]	< .001
Current psychological Distress (K-10)	18.11 ± 6.58	21.92 ± 8.86	1.06	1.03 – 1.08	5.01 [a]	< .001
Precipitating factor to first episode						
Out of the blue	116 (12.00)	48 (12.09)				
Death of someone close	200 (20.68)	79 (19.90)	1.32	.74 – 2.35	.96	.342
Stress	651 (67.32)	270 (68.01)	1.00	.58 – 1.70	-.02	.988

OR, odds ratio; CI, confidence interval; SD, standard deviation

Coding: chronic (1.00) non-chronic (0.00)

[a] Significant finding after Bonferroni adjustment

[b] Missing data on variable due to participants not reporting number of episodes of depression

4.4.2 Clinical features. Individuals with CD had a younger age of onset and more frequent episodes of depression compared to NCD individuals. Individuals with CD also had higher levels of disability, more traumatic events experienced in their lifetime, more chronic medical conditions and higher psychological distress compared to individuals with NCD. Table 4.2 displays the clinical features associated with CD.

4.4.3 Psychiatric co-morbidity. The CD sample had a greater number of lifetime co-morbid psychiatric disorders than NCD individuals (see Table 4.2). In particular, CD individuals had significantly higher rates of post-traumatic stress disorder, generalised anxiety disorder and obsessive–compulsive disorder (see Table 4.3). Chi square analyses determined no significant differences between the two groups in terms of the temporal sequence of the development of the co-morbid disorders and their depression (see Table 4.3). The onset of CD and the development of lifetime DSM-IV co-morbid disorders are depicted in Figure 4.1.

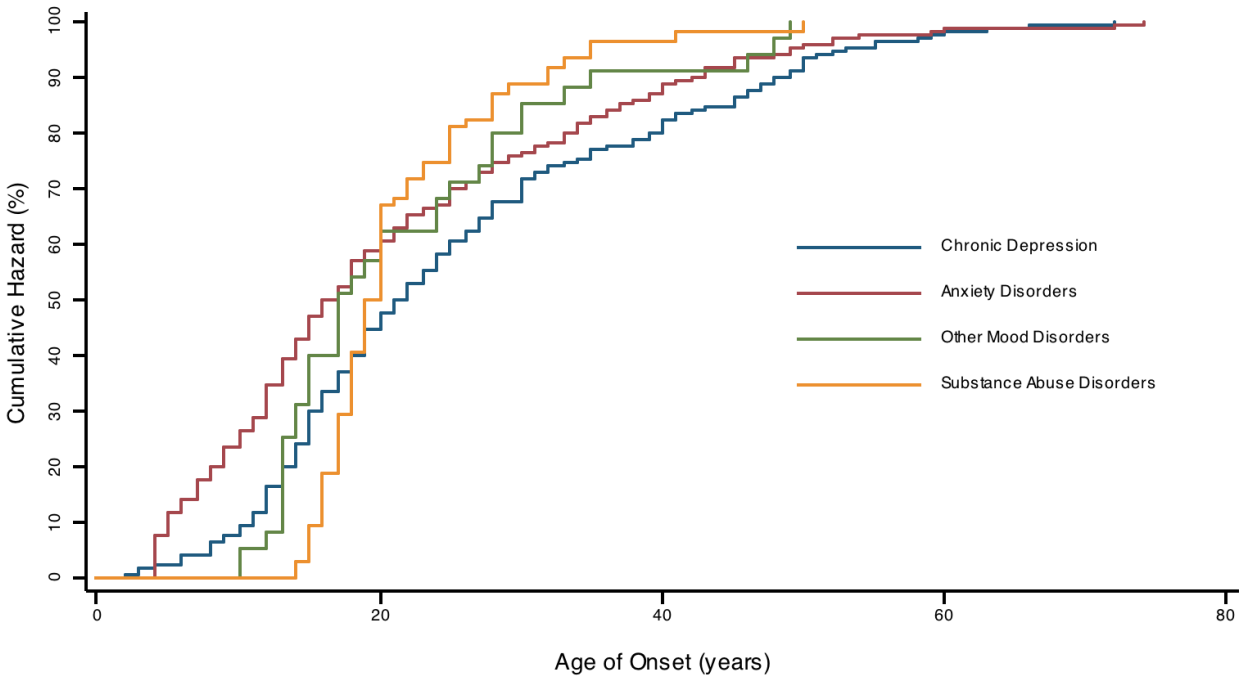


Figure 4.1. The age of onset of chronic depression (N = 398) and lifetime DSM-IV co-morbid mental disorders

4.4.4 Correlates of chronic depression. Fifteen putative correlates of chronic depression were entered into a multivariable logistic regression model (see Table 4.4). The goodness-of-fit of the multivariable model was tested with the Hosmer–Lemeshow statistic and found to be satisfactory ($\chi^2 = 3.89$, df = 8, p = .87). The model correctly classified 77.3% of individuals with a

sensitivity of 38.8% and specificity of 92.2%. The area under the receiver operating characteristic (ROC) curve was .78 (95% CI: .75–.80). Five factors were found to be significant correlates of chronic depression: a greater number of co-morbid psychiatric disorders (χ^2 = 32.95, p<.001); older current age (χ^2 = 25.00, p<.001); younger age of onset (χ^2 = 16.08, p<.001); more frequent episodes of depression (χ^2 = 5.11, p<.027); and the first episode of depression occurred after the death of someone close rather than out of the blue (χ^2 = 5.66, p<.021). There was no evidence of multicollinearity between the variables as indicated by the mean Variance Inflation Factor (VIF) of 1.46 and Tolerance values above 0.1. The model was found to be significant (likelihood ratio test χ^2 = 279.61, p <.001) and the odds ratios of all correlates are presented in Table 4.4.

4.4.5 Perceived need for mental health services. Approximately 42.2% of CD individuals (N = 168) and 59.4% of NCD individuals (N = 574) believed that they had no need to utilise the mental health services that were available to them. After adjusting for chronicity, no difference was found between individuals who felt they had no need to utilise services and individuals who did feel the need to access services on their self-reported hopelessness score (OR = .82; 95% CI .64–1.06; t =−1.56; p =.125). On their self-reported worthlessness score, adjusting for chronicity, individuals who felt no need to access services had a significantly lower worthlessness score than individuals who felt the need to access services (OR =.65; 95% CI: .51–.84; t = −3.40; p<.001).

4.4.6 Health service utilisation. During their lifetime, 81.2% of individuals with CD (N = 323) and 75.7% of individuals with NCD (N =732) had a consultation with a health professional about their mental health (including GP, psychiatrist, mental health nurse, psychologist). In particular, 70.9% of individuals with CD (N = 282) and 64.4% of those with NCD (N = 623) had consulted a general practitioner (GP; primary care physician) about their mental health problems (OR = 1.21; 95% CI 0.73–1.71). There was no significant difference between the two groups on whether they had consulted a general practitioner (GP; primary care physician) about their mental health problems. Individuals with CD (40.7%; N = 162) were more likely to have had a consultation with a psychiatrist during their lifetime compared with non-chronic individuals (25.5%; N = 247; OR = 1.62; 95% CI 1.11–2.38). Despite CD individuals being more likely to see a psychiatrist, there was no difference between CD (N = 246; 61.81%) and NCD individuals (N = 513; 53.05%) on whether they had received prescription medication for mental health problems (OR = .87; 95% CI .60–1.27). There were also no significant differences between CD individuals (N = 85; 21.36%) and NCD individuals (N = 123; 12.72%) on whether they had been hospitalised for their depression (OR = 1.95; 95% CI .99 – 2.58).

Table 4.3

Lifetime co-morbid diagnoses for individuals with chronic and non-chronic depression

							Temporal Relationship Between Onset of Chronic/Non-Chronic Depression and Co-morbidities [a]					
	Lifetime Prevalence of Co-morbidity [a]						Chronic Depression (N = 398)			Non-Chronic Depression (N = 967)		
Co-morbid Disorder	Non-Chronic (N = 967) N (%)	Chronic (N=398) N (%)	OR	95% CI	t	p	CD first N (%)	Other disorder first N (%)	Same Year N (%)	NCD first N (%)	Other disorder first N (%)	Same Year N (%)
Post Traumatic Stress	201 (20.79)	133 (33.42)	2.16	1.57– 2.98	4.78[b]	<.001	68 (51.13)	45 (33.83)	20 (15.04)	67 (33.33)	94 (46.77)	40 (19.90)
Agoraphobia	44 (4.55)	37 (9.30)	1.84	1.01 – 3.36	2.03	.047	8 (21.62)	15 (40.54)	14 (37.84)	10 (22.72)	25 (56.82)	9 (20.45)
Social Phobia	255 (26.37)	152 (38.19)	1.58	1.06 – 2.36	2.32	.024	27 (17.76)	99 (65.13)	26 (17.11)	28 (10.98)	192 (75.29)	35 (13.73)
Panic	107 (11.07)	67 (16.83)	1.62	.99 – 2.65	1.94	.057	24 (35.82)	21 (31.34)	22 (32.84)	19 (17.76)	38 (35.51)	50 (46.73)
Generalised Anxiety	239 (24.72)	220 (55.28)	3.43	2.41 – 4.87	7.01[b]	<.001	83 (37.73)	58 (26.36)	79 (35.91)	64 (26.78)	77 (32.22)	98 (41.00)
Obsessive Compulsive	89 (9.20)	48 (12.06)	2.29	1.37 – 3.82	3.24[b]	<.002	17 (35.42)	22 (45.83)	9 (18.75)	31 (34.83)	45 (50.56)	13 (14.61)
Bipolar I	33 (3.41)	21 (5.28)	1.57	.57– 4.33	.88	.381	14 (66.67)	3 (14.29)	4 (19.05)	20 (60.61)	4 (12.12)	9 (27.27)
Bipolar II	32 (3.31)	19 (4.77)	1.51	.52 – 4.45	.77	.444	10 (52.63)	3 (15.79)	6 (31.58)	18 (56.25)	6 (18.75)	8 (25.00)
Substance Abuse	79 (8.17)	36 (9.05)	1.00	.58 – 1.74	.01	.992	24 (66.67)	10 (27.78)	2 (5.56)	27 (34.18)	41 (51.90)	11 (13.92)
Substance Dependence	131 (13.55)	74 (18.59)	1.04	.65 – 1.68	.18	.859	42 (56.76)	25 (33.78)	7 (9.46)	45 (34.35)	69 (52.67)	17 (12.98)

OR, odds ratio; CI, confidence interval

Coding: chronic (1.00) non-chronic (0.00)

[a] Adjusted for age at interview

[b] Significant finding after Bonferroni adjustment

Table 4.4

Multivariate logistic regression model predicting lifetime chronic depression

Predictor	OR	CI (95%)	t	p
Current age (years)	1.04	1.02 – 1.05	5.00 [a]	< .001
Female gender	1.00	.63 – 1.57	-.02	.985
Greater number of episodes (> 3)	1.75	1.07 – 2.86	2.26 [a]	< .027
Unemployment	1.60	.97 – 2.64	1.87	.067
Suicidal ideation	1.05	.52 – 2.14	.15	.883
Suicide attempt(s)	.61	.33 – 1.12	-1.62	.110
Psychiatric co-morbidity	1.42	1.26 – 1.61	5.74 [a]	< .001
Medical co-morbidity	1.04	.94 – 1.15	.81	.420
Traumatic load	1.02	.92 – 1.12	.33	.741
Current disability (WHODAS12)	1.01	.99 – 1.03	.97	.338
Current psychological distress (K-10)	1.02	.97 – 1.06	.74	.464
Severe symptoms	1.14	.60 – 2.18	.42	.678
Age of onset (years)	.97	.95 - .98	-4.01 [a]	< .001
Precipitating factor of first episode				
Out of the blue	*reference category*			
Death of someone close	2.60	1.16 – 5.79	2.38 [a]	< .021
Stress	1.48	.79 – 2.78	1.24	.221
No. of family members with depression	.99	.75 – 1.32	-.05	.959

OR, odds ratio; CI, confidence interval

Coding: chronic (1.00) non-chronic (0.00)

[a] Significant finding

4.4.7 Health services utilisation by individuals with chronic depression. The majority of individuals with CD had received primary care treatment, defined as a lifetime consultation with a health professional and/or prescription medication for mental health (N = 247; 62.0%). A smaller proportion of individuals with CD had received both inpatient and outpatient treatment (tertiary care) for their depression (N = 85; 21.4%). The remaining CD individuals (N = 66; 16.6%) reported no formal treatment for depression and were thus classified as untreated. Individuals with CD who reported that they had never had a lifetime consultation with any professional for their mental health, who had never been hospitalised for their depression and who had never received prescription medication for their mental health were classified as untreated. Table 4.5 shows the comparisons between the three health service utilisation groups (tertiary care, primary care and untreated) in CD.

Chronically depressed individuals who were treated in tertiary care were more likely to be female and unemployed compared to individuals treated in primary care and untreated individuals. Untreated individuals were more likely to be male, have a later age of onset and have an older current age. Individuals treated in tertiary care settings had a greater number of episodes of depression, more severe symptoms, a greater family history of depression, greater psychiatric co-morbidity, a greater traumatic load, higher levels of disability and higher levels of current psychological distress. During their lifetime, individuals treated in tertiary care were also two to three times as likely to attempt suicide (N = 44; 51.76%) compared with individuals treated only in primary care (N = 34; 13.8%) and untreated individuals (N = 4; 6.06%). These findings suggest that chronically depressed individuals treated in tertiary care settings have a much more complex presentation than chronically depressed individuals treated in primary care and untreated chronically depressed individuals.

Table 4.5

Sociodemographic and clinical differences between individuals with chronic depression and varying levels of health service utilisation (primary, tertiary and untreated)

Feature	Tertiary care (N = 85) N (%) / Mean ± SD	Primary care (N = 247) N (%) / Mean ± SD	Untreated (N = 66) N (%) / Mean ± SD	Test statistic ANOVA (F) or Chi-square (χ^2)
Age (years)	46.99 ± 15.83	45.89 ± 14.56	52.59 ± 16.80	F (2, 395) = 5.05, p <.007
Gender				
Female	62 (72.94)	165 (66.80)	35 (53.03)	
Male	23 (27.06)	82 (33.20)	31 (46.97)	χ^2 (2) = 6.82 p <.033
Education				
Tertiary	22 (25.88)	92 (37.25)	16 (24.24)	
High school level	46 (54.12)	115 (46.56)	35 (53.03)	
Skilled vocation	17 (20.00)	40 (16.19)	15 (22.73)	χ^2 (2) = 6.63 p .157
Employment Status				
Employed	30 (35.29)	145 (58.70)	34 (51.52)	
Unemployed	55 (64.71)	102 (41.30)	32 (48.48)	χ^2 (2) = 13.93 p <.001
Number of episodes				
Fewer no. of episodes (≤ 3) [b]	25 (32.47)	96 (42.29)	37 (58.73)	
Greater no. of episodes (> 3) [b]	52 (67.53)	131 (57.71)	26 (41.27)	χ^2 (2) = 9.89 p <.007
Age of Onset (years)	24.23 ± 13.48	24.54 ± 13.71	29.79 ± 17.38	F (2, 394) = 3.82, p <.023
Symptom Severity				
Non-Severe symptoms	5 (5.88)	56 (22.67)	21 (31.82)	
Severe symptoms	80 (94.12)	191 (77.33)	45 (68.18)	χ^2 (2) = 16.98, p <.001
No. of Family Members with Depression	.75 ± 1.08	.68 ± .91	.24 ± .46	F (2, 395) = 7.35, p <.001
Suicidal ideation				
No	19 (22.35)	115 (46.75)	43 (65.15)	
Yes	66 (77.65)	131 (53.25)	23 (34.85)	χ^2 (2) = 28.77, p <.001
Previous suicide attempt(s)				
No	41 (48.24)	212 (86.18)	62 (93.94)	
Yes	44 (51.76)	34 (13.82)	4 (6.06)	χ^2 (2) = 65.78 p <.001
No of. co-morbid psychiatric disorders	5.31 ± 2.23	4.02 ± 2.05	2.91 ± 1.83	F (2, 395) = 25.90 p <.001
No of. co-morbid medical conditions	3.54 ± 2.88	2.94 ± 2.38	2.68 ± 2.37	F (2, 395) = 2.59, p = .076
Traumatic load	5.47 ± 4.00	3.94 ± 3.00	3.12 ± 2.61	F (2, 395) = 16.16, p <.001
Current disability (WHODAS12)	26.63 ± 19.88	20.08 ± 18.30	16.13 ± 17.87	F (2, 394) = 6.46, p <.002
Current psychological Distress (K-10)	24.48 ± 10.09	22.12 ± 8.36	17.89 ± 7.64	F (2, 395) = 10.95, p <.001

4.5 Discussion

In the present study, the lifetime prevalence of chronic depression in community-residing individuals in Australia was 4.6%. A recent United States (U.S.) study which was based on data from the Healthcare for Communities (HCC) survey had a comparable reported lifetime prevalence of persistent depression of 4.0% (Young, Klap, Shoai, & Wells, 2008). The prevalence of chronic depression in both Australia and the United States is considerably higher than the reported Canadian lifetime prevalence of 2.7%, which was derived from the Canadian Community Health Survey: Mental Health and Well-Being (2002) (Satyanarayana, Enns, Cox, & Sareen, 2009). The lower lifetime prevalence of chronic depression in the Canadian survey is likely to be the consequence of it not including individuals with Dysthymic Disorder. The inclusion of individuals with Dysthymic Disorder makes the present study more clinically relevant to the new DSM-5 diagnosis of Persistent Depressive Disorder.

The current study found that higher rates of psychiatric co-morbidity, older age, a younger age of onset, more frequent episodes of depression and a first episode of depression that developed after the death of someone close were significant correlates of chronic depression. In line with previous findings, greater psychiatric co-morbidity had the strongest association with chronic depression (Satyanarayana, Enns, Cox, & Sareen, 2009). The link between chronicity and complex psychiatric co-morbidity is well established (Bagby, Psych, Quilty, & Ryder, 2008; de Graaf, Bijl, Ten Have, Beckman, & Vollebergh, 2004) and could be viewed as a vulnerability that precedes chronic depression, a complication due to chronicity, or as a modifier that influences the presentation of the depressive episode (Bagby, Psych, Quilty, & Ryder, 2008).

Anxiety disorders were the most common co-morbid conditions, with chronically depressed individuals having higher rates of generalised anxiety disorder, obsessive compulsive disorder and post-traumatic stress disorder compared to non-chronically depressed individuals. These findings are consistent with previous work that found anxiety disorders to be the most common co-morbid disorders with MDD (de Graaf, Bijl, Ten Have, Beekman, & Vollebergh, 2004; Rush, et al., 2005). Individuals may have a biological predisposition to both a chronic course of depression and more anxiety features.

The “kindling” hypothesis has been used to investigate the relationship between recurrent episodes of depression and chronicity. This hypothesis suggests that life stress is strongly associated with the first episode of depression rather than recurrent episodes of depression (Monore & Harkness, 2005). It is thought that recurrent episodes may emerge autonomously to stress where stress is no longer required to precipitate an episode (Monroe & Harkness, 2005). Alternatively, recurrence may be due stress sensitisation where even minor stress may trigger the onset of a

depressive episode (Monroe & Harkness, 2005). The current study found that chronic depression was associated with a greater number of episodes and a first episode of depression precipitated by the death of some close. Chronic depression was also associated with a greater lifetime traumatic load and a higher prevalence of PTSD in the bivariate analyses. These findings may provide support for the kindling hypothesis and may suggest that the effect is more evident in individuals with chronic depression than non-chronic depression.

A younger age of onset was also a significant correlate of chronic depression. Some investigators have suggested that an earlier age of onset is indicative of a more chronic course of depression and is a heterogeneous feature among all chronic depressive subtypes (Klein, 2010). In keeping with the findings of others (Gilmer, et al., 2005; Rush, Laux, Jarrett, Weissenburger, Feldman-Koffler, & Stone, 1995), we found that older current age was associated with increased risk of lifetime chronic depression. This might be a temporal exposure artefact, as older people have had a longer time to manifest chronic depression, a condition with a variable age of onset. Alternatively, chronic depression might be linked to older age or to some unmeasured factor linked to older age. We favour the former explanation because most epidemiological studies demonstrate falling rates of depression among community-residing older people (Charles, Reynolds, & Gatz, 2001; Kessler, Birnbaum, Bromet, Hwang, Sampson, & Shahly, 2010a). However, cerebrovascular disease, including stroke and white matter ischemic changes, is associated with older age, a chronic course and treatment resistance of depression (Rao, 2000; Sheline, et al., 2010).

The overall lifetime prevalence of self-reported mental health service use for individuals with affective disorders in Australia is 58.6% (Burgess, Pikis, Slade, Johnston, Meadows, & Gunn, 2009). In the current study, most of the non-chronically and chronically depressed individuals had seen a general practitioner (primary care practitioner) about their mental health problems during their lifetime, but less than half of the chronically depressed individuals reported consultations with a psychiatrist during their lifetime. In relation to this finding, it is worth noting that Australia has a universal health insurance system that covers both primary and secondary care. A recent U.S. multi-site study of the adequacy of prior antidepressant treatment found that despite high symptom severity and a chronic course of depression, only one third of chronically depressed individuals had ever received an adequate antidepressant trial (Kocsis, et al., 2008). The current study found that 42.2% of chronically depressed individuals felt they had no need to utilise the mental health services that were available to them. The nature and accessibility of mental health services may need to be modified to target chronic depression more effectively.

The current study identified that 16.6% of individuals with chronic depression were untreated. This was defined as reporting that they had never had a consultation with any health professional about mental health, had never received prescription medication for mental health and

had never been in hospital for their mental health during their lifetime. Individuals who were untreated were more likely to be male, have an older age of onset of depression and an older current age at time of assessment. Individuals who were treated in tertiary care (hospitalised for their depression) had a more complex presentation compared to untreated individuals and individuals treated in primary care only. These chronically depressed individuals with higher health service utilisation may indicate a greater severity of symptoms but also poorer response to treatment. However, this cannot be confirmed using data from the 2007 NSMHWB as historical treatment information and detailed hospital admission data were unavailable.

There are features of chronically depressed individuals treated in tertiary care that may indicate TRD. In particular the following features have been acknowledged in medical scientific literature as characteristic of TRD and have been found in chronically depressed individuals treated in tertiary care: greater number of episodes of depression (Dudek, et al., 2010; Sagud, et al., 2013), greater severity of depression (Souery, et al., 2007); higher levels of medical and psychiatric co-morbidity (Souery, et al., 2007; Amital, et al., 2013); greater traumatic load (Amital, et al., 2013; Kaplan & Klientob, 2000); higher levels of disability (Amital, et al., 2013; Petersen, et al., 2004); and are more likely to attempt suicide (Sagud, et al., 2013; Souery, et al., 2007; Pfeiffer, Kim, Ganoczy, Zivin & Valenstein, 2013).

Some caveats are warranted. The model I developed in the current study had low sensitivity but a high specificity, indicating that other, unmeasured, factors are likely to be important in distinguishing between chronic and non-chronic depression. These may include biological factors, personality traits and current psychosocial stressors. The nature of the secondary analysis, which was based on cross-sectional self-report data elicited by trained lay interviewers using structured interviews, did not allow for a detailed depiction of the course of chronic depression. Also, the cross-sectional data collection did not allow for a detailed analysis of the temporal relationship between the chronicity of depression and many clinical variables. There were also some inherent limitations in the definition of chronic depression that we employed and in the variable we used to split those individuals with lifetime MDD into chronic and non-chronic types of depression. However, the variable was chosen in line with the WMH-CIDI 3.0 recommendation for identifying persistence and also because the variable had been used to identify chronicity in an earlier Canadian study (Satyanarayana, Enns, Cox, & Sareen, 2009). The inclusion of individuals with a lifetime history of Bipolar Affective Disorders is consistent with the DSM-5 diagnosis of Persistent Depressive Disorder but may limit the comparability of the current paper with earlier chronic depression literature. However, the inclusion of individuals with a lifetime history of Bipolar Affective Disorder improves the generalisability of the paper to the general population in which co-morbid diagnoses are highly prevalent. The survey relied heavily on personal recall and it is unclear

the extent to which current symptoms or underlying negative temperament might have affected recall.

Despite these limitations, the significant differences identified between chronic and non-chronic depression, and the evidence of higher current disease burden with lifetime chronicity, lend support to the DSM-5 diagnosis of Persistent Depressive Disorder. As others have suggested (Klein, Shankman, & Rose, 2006; McCullough, et al., 2003), there may be some utility in collapsing the various chronic depressive subtypes into one entity, which focuses on the chronicity of the depressive presentation rather than on episodic and remitting features. The levels of psychological distress, functional disability and disease burden posed by chronic depression are considerable. The existence of a distinct nosological category of Persistent Depressive Disorder might facilitate greater public health emphasis on this high-prevalence condition.

Chapter Five

Research Methodology B: Clinical Data

5.1 Introduction

This chapter and the two that follow it deal with primary analyses of inpatient clinical data on treatment-resistant depression (TRD). Following the systematic review of the concept of TRD in Chapter Two, the next step was to estimate the prevalence and further characterise TRD at the national population level. The 2007 NSMHWB appeared to provide the opportunity to do this. However, TRD as it is generally conceptualised was not identifiable in the NSMHWB data set due to the limited treatment information collected in the survey. However, it was possible to investigate the prevalence and correlates of a closely related phenomenon, chronic or persistent depression (see Chapter Four). Using the 2007 NSMHWB it was possible to assess differences in health service utilisation and the characteristics of chronically depressed individuals who seek high health services (i.e. tertiary care settings). Chronically depressed individuals in the community who seek high-level health services may overlap to some extent with patients with TRD found in inpatient settings. Thus Chapters Six and Seven examine the degree of TRD and factors associated with particular levels of resistance in a sample of depressed inpatients. The purpose of this chapter is to detail the study design, setting, sample size, procedure, inclusion/exclusion criteria, measures, statistical analysis and ethical considerations of the research in Chapters Six and Seven.

5.2 Study Design

A cross-sectional cohort study was employed to explore the conceptualisation and clinical correlates of TRD. The purpose of this study design was to sample an inpatient cohort and retrospectively assess the history of exposures and other associations (Hudson, Pope, & Glynn, 2005). As described in more detail below, a convenience sample of male and female inpatients with Major Depressive Disorder was recruited from a private psychiatric hospital. Data were collected from four main sources (interviews and other clinical assessments conducted by the candidate, self-report questionnaires completed by the patients, informant questionnaires completed by an informant and clinical chart audits conducted by the candidate). The known complexity of TRD made the use of multiple sources of data imperative. This strategy was used to increase the likely reliability and validity of the findings. In addition, the study was designed to be naturalistic in order to assess the degree of TRD in a sample of inpatients in a tertiary care setting. All available, consenting, patients with MDD were recruited without using treatment resistance as an inclusion criterion. If a predetermined definition of TRD (e.g. the failure of two antidepressant trials) had been used as an inclusion criterion, it would **not** have been possible to validate existing models of

treatment resistance. Thus, by including all patients with MDD with varying levels of TRD as rated by the four available models of TRD, it allowed assessment of the degree of TRD in the sample and validation of the four existing models of TRD. More information on the inclusion and exclusion criteria can be found in the upcoming section, *5.5.1 Recruitment*.

5.3 Setting

It has been estimated that eight percent of the Australian population received public or private mental health services during 2009-2010 (AIHW, 2012). Mental health services in Australia include public and private, hospitalisation, residential care, hospital based outpatient services and community mental health, serviced by specialists and general practitioners (GP) (AIHW, 2012). In Australia, private hospitals provide care for patients with private health insurance or for patients covered by other funders (e.g. Workers Compensation or Department of Veteran Affairs). In 2011, 45% of the Australian population had private health insurance allowing access to private healthcare (Australian Bureau of Statistics, 2012). Private hospitals accounted for 17.4% of the available specialised mental health beds in Australia during 2009-2010 (Australian Bureau of Statisitics, 2010).

The primary data for this thesis were collected from a private psychiatric hospital, the New Farm Clinic, located in Brisbane, Australia. New Farm Clinic is owned and operated by Ramsay Healthcare and services not only the metropolitan Brisbane area but also the inner and outer regional areas in the state of Queensland. The hospital has 90 beds for acute inpatient care, an Electroconvulsive Therapy (ECT) suite, community outreach services and consulting suites for outpatient care. The research protocol and procedures were reviewed and approved by the University of Queensland Medical Research Ethics Committee (ethics approval number: 2010001485) and the New Farm Clinic Medical Advisory Committee (MAC) (see Appendix 3).

5.4 Sample Size

A sample size calculation was based on chronic depression data from the 2007 NSMHW 2007. Early in the planning and design phase of the research, logistic regression analyses were planned. For most purposes, the minimum sufficient sample size for logistic regression analyses is usually considered to be 100 and almost all such analyses can be undertaken with a sample size of no more than 500 (Long, 1997). A logit power analysis using the Stata command *powerlog* was modelled using an alpha of .05, a beta of .80 and an estimated squared multiple correlation between the predictors of .2. It was necessary to model the distribution of the likely predictor variable of *age*

from the 2007 NSMHW chronic depression data set. The result of the logit power analysis was a total predicted sample size of 162.

Due to the constraints of PhD research and the difficulties recruiting depressed individuals while in hospital for treatment the sample size target of 162 was not met. Seventy inpatients with a DSM-IV diagnosis of MDD were recruited in the available time. The participants are described in further detail in the subsequent empirical chapters.

5.5 Procedure

5.5.1 Recruitment. Between March 2011 and October 2012, 120 inpatients at the New Farm Clinic over the age of 18 diagnosed with DSM-IV MDD on admission by their treating psychiatrist were approached for inclusion to the research outlined in the subsequent results chapters. Twelve consultant psychiatrists at New Farm Clinic were asked to inform their patients with MDD who they deemed appropriate to participate, about the research study. In total 120 inpatients were deemed appropriate to recruit by their treating psychiatrist. Of those 120 patients, 70 patients (58.3%) provided informed consent and participated in the research study. The remaining inpatients (N = 50; 41.7%) were not recruited due to the following reasons: declining the invitation to participate, were deemed too unwell to participate, had a differential diagnosis of Bipolar I or II and/or discharged prematurely before providing informed consent.

If a patient expressed an interest in participating to their psychiatrist, the researcher approached the patient with a participant information and consent form required for participation. The research was described orally and the right to withdraw from the study at any time was reiterated. Individuals were given 24 to 48 hours to consider participating in the research and were encouraged to discuss their participation with their psychiatrist, family and/or friends. If an individual agreed to participate in the research they were asked to give written informed consent.

Patients were only approached for inclusion into the study with the approval of their treating psychiatrist and at time during their admission when the patient was deemed well enough to participate as determined by their treating psychiatrist and/or nursing staff on a daily basis. This resulted in all participants being approached for recruitment and interviewed not necessarily at the beginning of their admission but during their admission when they were considered to be stable and well enough to participate.

5.5.2 Inclusion and exclusion criteria. As Chapter Two emphasised, there was major variability in the inclusion/exclusion criteria employed by investigators in RCTs of TRD. In addition, Chapter Two (see *2.5 Discussion*) refers to Rush, Thase and Dube (2003) who state that

"excluding most co-morbid disorders would improve the homogeneity of studies but reduce the generalizability of the findings in clinical populations". Thus inclusion and exclusion criteria were used in an attempt to recruit a "real-world" sample of patients with MDD. Inclusion and exclusion criteria are summarised in Table 5.1 and discussed in detail below. The primary inclusion criterion was a DSM-IV diagnosis of MDD on admission made by the participants' treating psychiatrist (see Table 5.1). In line with DSM-IV diagnosis of MDD, participants whose symptoms were better accounted for by a general medical condition or from substance use were excluded.

5.5.2.1 Antidepressant medication on study entry. No required dose or duration of the participants' current antidepressant trial was required for inclusion. This approach was used because it was possible that participants would be admitted to hospital for medication changes or would have medication changes throughout their admission resulting in lower than standard doses or a dose duration under 4 weeks when recruited into the study. Nominating a required dose or duration of current antidepressant treatment was not considered as an inclusion criterion as the primary aim of the thesis was to determine lifetime TRD retrospectively not current episode TRD. Additionally, response to current antidepressant treatment was not a primary outcome measure of the research.

5.5.2.2 Treatment resistance. A minimum level of TRD was not required for inclusion into the research study. One of the primary aims of the study (see **Research Question 4**) was to determine the degree of TRD in a sample of depressed inpatients. The study was designed to obtain a naturalistic or "real-world" sample without a predefined definition of TRD applied to the sample as an inclusion criterion. As highlighted in the introduction and early chapters of the thesis, no standardised definition of TRD has been universally adopted in medical scientific literature or clinical practice. The benefit of not defining TRD and including a naturalistic sample of participants with varying levels of TRD is that the five models of TRD can be validated in the one study (which, to the writer's knowledge, has previously not been attempted in medical scientific literature). As the majority of models and definitions of TRD are theoretical without adequate empirical validation, if a predefined definition of TRD was applied to the sample it would limit the thesis to drawing conclusions about one interpretation of TRD rather than providing the opportunity to review multiple TRD constructs.

5.5.2.3 Bipolarity. There is a strong consensus in the contemporary medical scientific literature that individuals with a diagnosis of Bipolar I or II should be excluded from clinical trials in TRD. Fifty (34%) of the RCTs reviewed in Chapter Two excluded individuals with Bipolar I or II on the basis that bipolar depression is nosologically distinct from unipolar depression. Additionally, there is evidence to suggest a link between bipolarity and what has been called "pseudoresistance" due to misdiagnosis (Bader & Dunner, 2007, Dudek, et al., 2010; Kiejna, et al.,

2010). Therefore, to improve conceptual clarity, bipolar depressed patients were excluded from the current study (see Table 5.1).

5.5.2.4 Axis II Disorders. Patients with a co-mobrbid Axis II Personality Disorder, as diagnosed by their treating psychiatrist, were included in the study. As mentioned previously, the aim of the thesis was to reruit a "real-world" sample of inpatients and provide findings which are relevant to clincal practice. Including patients with MDD and co-morbid Axis II Personality Disorders was essential in a "real-world" sample of TRD as co-morbid Axis II Personality Disorders are common in patients with MDD (Fava et al., 2002) and have been linked to poorer treatment outcomes (cited in Kornstein & Schneider, 2001). The presence of Axis II Personality Disorders in the sample was not independently assessed and the diagnoses reported in the following results chapters were reliant on the treating psychiatrists' diagnoses and medical chart auditing. Although a standardised measure of Axis II Personality Disorders would have been preferrable, a self-report measure of personality was employed in order to assess personality functioning in the sample. During the deisgn phase of the research, a dimensional assessment of personality functioning (using a self-report measure) was decided apon as the DSM-5 workgroup were considering removing the categorical Axis II diagnostic system and implementing a dimensional assessment of maladatpive personality functioning (Skodol, 2012).

5.5.2.5 Psychotic features. Patients with a DSM-IV diganosis of MDD with psychotic features and/or lifetime history of a psychotic disorder as diagnosed by their treating psychiatrist were also excluded. Approximately 40% (N = 60; 40.2%) of studies in the systematic review detailed in Chapter Two excluded psychotic features or psychotic disorders from RCTs on TRD (see *2.4.6 Psychiatric exclusion criteria*). Not only is it a consenus in medical scientfic literature to exclude psychotic disorders and psychotic features from studies on TRD it also poses potential ethical challenges in regards to informed consent when recruiting patients with active psychotic symptoms. During the design phase of the research project, it was decided to exclude patients with a DSM-IV diganosis of MDD with psychotic features and/or patients with a lifetime history of a psychotic disorder as diagnosed or documented by their treating psychiatrist.

Table 5.1

Inclusion and exclusion criteria

Inclusion	Exclusion
• Over 18 years old • DSM-IV diagnosis of Major Depressive Disorder on admission by treating psychiatrist • Approval from treating psychiatrist to be involved in research study	• Current psychotic features and/or lifetime history of a psychotic disorder • A current or lifetime DSM-IV diagnosis of Bipolar I or II disorder • Acute safety risk or deemed too unwell by treating psychiatrist or nursing staff

5.5.3 Informed consent and safety considerations. The ethical considerations surrounding informed consent and the recruitment of a vulnerable population of participants are discussed in section *5.7 Ethical Considerations*. A mandatory protection factor for this population is the exclusion patients who cannot provide or do not have the capacity to provide informed consent. An additional exclusion criterion was that any patient who was deemed too unwell to participate or who posed an acute safety risk to themselves or others was either excluded entirely or not recruited until such a time during their admission when they were deemed appropriate to participate by their treating psychiatrist. Approval from the treating psychiatrist was also sought for all participants recruited into the study in order to protect the participant and keep the treating psychiatrist informed of any adverse effects related to the study.

After informed consent was obtained, participants were asked to participate in an interview, psychological and cognitive assessments, a medical record chart audit and nominate an informant to complete questionnaires about their pre-morbid personality.

5.5.4 Medical record chart audit. Treatment and clinical information was retrieved from participants' medical records via medical record chart auditing. In particular, information about current and previous antidepressant treatment, electroconvulsive therapy (ECT), psychotherapy and other treatments was retrieved from medical records. Important clinical and socio-demographic information was also collected. Table 5.2 presents an overview of the information collected from medical record chart auditing.

5.5.5 Interview and assessment. All interviews and assessments (see Table 5.3) were conducted by the candidate, who was a graduate in psychology with accredited training in conducting the WMH-CIDI 3.0. After informed consent was obtained, participants were interviewed using the WMH-CIDI 3.0 to confirm a diagnosis of MDD and depression course, and to confirm socio-demographic details retrieved from chart audits. Details such as age, employment

status, education, marital status, sexual orientation, age of onset of depression, number of episodes of depression, suicide events, medical co-morbidity and treatment information was obtained and confirmed. Psychological and cognitive assessments were also administrated during the interview (see Table 5.3). The following section (*5.6 Measures*) provides an overview and the psychometric properties of each assessment instrument.

Interviews were conducted with the participants' care in mind and were planned to take approximately 2 – 2 ½ hours. Interviews were administrated over several sessions to provide adequate breaks for participants. In addition, interviews were scheduled around the day-to-day activities of the hospital, psychotherapy groups and visitors to the hospital.

5.5.6 Self-reported questionnaires. After the interview and psychological assessments were completed, participants were asked to complete self-reported questionnaires in their own time. Participants were asked to take their time in completing the questionnaires and to contact the researcher if they required help or if they were experiencing any adverse emotional or psychological effects from the questions. At the completion of the interview and after the researcher left the questionnaire booklet with the participant, the nursing staff were informed in the event of any adverse emotional effects or worsening of mental state from the questioning. The researcher checked in with the participant frequently while they completed the questionnaire booklet. Table 5.3 lists each self-reported questionnaire. Additional information on each measure is provided in the forthcoming section (*5.6 Measures)*.

Table 5.2

Information retrieved from medical chart auditing

Type of information	Details
Current and previous antidepressant treatment	Antidepressant name/ type Dose Duration
Electroconvulsive therapy (ECT)	ECT type (unilateral/bilateral) Number of ECT treatments Number of ECT courses
Psychotherapy	Type of psychotherapy (group or individual)
Other treatments received	Transcranial Magnetic Stimulation (TMS) Vagus Nerve Stimulation (VNS)
Clinical details	DSM-IV admission diagnosis Co-morbid psychiatric disorders Age of onset and illness course Self harm events Suicide attempts Family history of depression Medical history and co-morbid medical conditions Relevant life events e.g. trauma events Precipitating factors to depression
Admission Details	Number of admissions hospital Length of stay in hospital
Socio-demographic variables	Age Gender Marital status Employment status Sexual orientation

5.5.7 Informant questionnaire. Participants were asked to provide the contact details of an informant. More specifically, they were asked to nominate someone who had known them for at least 10 years, including periods when they had not been depressed. Nominated informants were sent an information sheet, consent form and questionnaire booklet. Informants were asked complete the informant version of the NEO-FFI (McCrae & Costa Jr, 2010) reflecting on the participants'

pre-morbid personality. Enclosed with the questionnaire booklet and consent form was a reply paid envelope for its return.

5.6 Measures (see Table 5.3)

5.6.1 World Mental Health Composite International Diagnostic Interview (WMH-CIDI 3.0). The WMH-CIDI 3.0 was used to confirm the primary diagnosis of MDD made by the participants' treating psychiatrist. The WMH-CIDI 3.0 was developed to generate diagnoses based on the diagnostic criteria of the WHO International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (Kessler & Ustun, 2004). It is the most widely used diagnostic interview in psychiatric epidemiological research and is useful for cross-national comparative research (Haro, et al., 2006). The WMH-CIDI 3.0 is expected to take 120 minutes in community samples and would take significantly longer in psychiatric populations with complex presentations. Because of this, only selected modules of the WMH-CIDI 3.0 were used in the present study. Only modules which confirmed the primary diagnosis of MDD, screened for co-morbidity, ruled out Bipolar I or II, assessed medical co-morbidity and socio-demographic details were administered.

Table 5.3

Administrated measures and self-reported questionnaires used to assess treatment resistance in the sample.

Assessments during interview	Hamilton Rating Scale for depression (HAM-D)
	Standardised Mini Mental State Examination (SMMSE)
	Hopkins Verbal Learning Test (HVLT)
	Trail Making Test B
Participant Questionnaires	NEO Five Factor Inventory (NEO-FFI)
	Kessler Psychological Distress Scale (K-10)
Informant Questionnaires	Informant version of the NEO Five Factor Inventory (NEO-FFI)

5.6.2 17-item Hamilton Depression Rating Scale (HAM-D) using the Structured Interview Guide for the HAM-D (SIGH-D). The 17-item HAM-D was administered using the Structured Interview Guide for the HAM-D (SIGH-D) during the interview and assessment phase of recruitment. The HAM-D using the SIGH-D was chosen for this research study as it is considered to be the "gold standard" measure for depression clinical research (Baer & Blais, 2009). The HAM-D (Hamilton, 1960) was developed in 1960 and revised in 1966, 1967, 1969 and 1980. The original purpose of the 17-item HAM-D was to test the effectiveness of the first generation antidepressants and it soon became the 'gold standard' measure of depression severity (Bagby, Ryder, Schuller, &

Marshall, 2004). The scale is clinician rated and several versions have been developed including both longer and shorter versions of the original 17-item scale. The internal reliability, convergent validity and discriminant validity have all been deemed adequate (Bagby, Ryder, Schuller, & Marshall, 2004). High inter-rater reliability of the HAM-D has been reported in novices (N = 21) with no previous experience administering the HAM-D (Muller & Dragicevic, 2003). The test-retest reliability is considered to be fair for individual items of the HAM-D with improvement in inter-rater reliability using the SIGH-D (Williams, 1988). The 17-item HAM-D incorporates both 3-point and 5-point response scales to rate items. The total score on the HAM-D can range from 0 to 54, with higher scores indicating more severe depression. A score between 0 and 6 indicates the absence of clinically significant depression, a score between 7 and 17 is considered to indicate mild depression, a score between 18 and 24 indicates moderate depression and scores over 24 indicate severe depression (Baer & Blais, 2010).

5.6.3 Kessler Psychological Distress Scale (K-10). The K-10 scale is a self-report measure that was developed to measure non-specific psychological distress experienced over a 30-day period (Kessler, et al., 2003). The K-10 has been used in multiple Australian population health surveys conducted by the Australian Bureau of Statistics such as the 1997 and 2007 National Survey of Mental Health and Wellbeing (see Chapter Four) and is currently in use by Beyond Blue as their primary online *Anxiety and Depression Checklist*. The widespread use of the K-10 in Australia and the potential opportunity to compare the sample of inpatients in Chapter Six and Seven with norms or depressed individuals in the community using the 2007 National Survey of Mental Health and Wellbeing justifies the use of the scale. Furthermore, the psychometric properties of the K-10 are sound with the K-10 showing good internal consistency and predictive validity (Kessler, et al., 2003). At this time, it appears that no published studies have assessed the test-retest reliability of the K-10.

The Australian version of the K-10 consists of 10 items rated on a 5-point scale ranging from 1 to 5, with 1 representing “none of the time” and 5 representing “all of the time” (Clinical Research Unit for Anxiety and Depression, 2000). The highest possible score is 50 and the lowest possible score is 10. Individuals who score under 20 are considered to be well. Scores between 20 and 24 indicate mild psychological distress, scores between 25 and 29 moderate psychological distress and scores above 30 indicate severe psychological distress (Clinical Research Unit for Anxiety and Depression, 2000).

5.6.4 Hopkins Verbal Learning Test (HVLT). Assessing verbal memory impairments in the sample was proposed as cognitive impairments and reduced performance across all neurocognitive domains has been reported in patients with TRD in a previous study (Gupta, et al., 2013). In addition, as described in section *5.3 Setting*, participants were recruited from a private

psychiatric hospital with an ECT suite. A past or current history of ECT treatment was not an exclusion criterion and it was expected that a number of recruited participants would have received ECT treatment for their depression. The use of ECT as a treatment for depression has been associated with cognitive abnormalities post treatment (Semkovska & McLoughlin, 2010). Furthermore, verbal memory and executive functioning impairments have also been reported in inpatients with recurrent depression and may indicate a chronic cognitive decline over time (Fossati et al., 2002) and be correlated with reported anatomical changes in recurrent depression such as hippocampal atrophy (see Chapter Six) (Sheline et al., 1996 cited in Fossati et al., 2002).

The HVLT was employed because it assesses immediate auditory verbal memory by requiring participants to recall a list of 12 words after each of three presentations of the list (Brandt, 1991; Benedict, Schretlen, Groninger, & Brandt, 1998). The HVLT has been used in previous studies investigating depression and cognitive performance (Olver et al., 2008; Semkovska & McLoughlin, 2010). Individuals are asked to listen carefully as the 12-word list is read and attempt to memorise the words. The number of words the individual is able to recall after each trial is recorded (minimum 0; maximum 12). The recall for each trial is summed to calculate a total immediate recall HVLT score (minimum 0; maximum 36). The HVLT has been shown to discriminate between individuals with mild cognitive impairment and healthy controls (de Jager, Schrijnemaekers, Honey, & Budge, 2009). A delayed recall trial, scored out of 12, can be subsequently administered although this was not employed in the present study.

5.6.5 Standardised Mental Mini Mental State Examination (SMMSE). The SMMSE is a measure of cognitive function that is widely used in dementia and depression studies (Vertesi et al., 2001). It is a quick measure of cognitive function and is commonly used in clinical practice (Vertesi et al., 2001). Many studies have reported the reliability and validity of SMMSE (Vertesi et al., 2001). It has adequate test-retest reliability and is able to measure the change in cognitive functioning over time (Vertesi et al., 2001). The SMMSE provides a global score of cognitive functioning and measures the following domains, orientation, registration, concentration, short-term recall, naming, ability to read and follow instructions and sentence construction (Vertesi et al., 2001). A score between 26 and 30 is considered normal cognitive functioning (Vertesi et al., 2001). Scores between 25 and 20 indicate mild cognitive impairment and scores between 20 and 10 indicate moderate impairment (Vertesi et al., 2001). Severe cognitive impairment is denoted by scores between 9 and 0.

5.6.6 Trail Making B. The Trail Making B assesses an individual's ability to visually search, scan, processing speed, mental flexibility and executive functions (Tombaugh, 2004). It is a test which is included in many cognitive batteries and is sensitive to cognitive impairments related to executive function, such as depression (Tombaugh, 2004). The test requires an individual to draw

connecting lines between 25 sequential numbers and letters alternating between the numbers and letters (e.g. 1 – A – 2 – B – 3 – C). The numbers and letters are distributed on a piece of paper requiring the individual to search for the required letter or number. The time (in seconds) it takes for the individual to complete the task is measured. The Trail Making B has been used in previous depression studies and compared to healthy controls (N = 49), inpatients with depression (N = 40) had slower Trail Making B test times (Ravnkilde et al., 2002). More specifically, the depressed inpatients had a mean Trail Making B score of 101 seconds (SD = 40.1) which was significantly slower than the healthy controls test score of 66.6 seconds (SD = 22.2) (Ravnkilde et al., 2002).

5.6.7 NEO Five-Factor Inventory (NEO-FFI). There has been longstanding interest in the role that co-morbid personality pathology plays in the course and outcome of depression (Morey, et al., 2010). However, the assessment of the underlying personality structure of patients with TRD has remained understudied (see Chapter Seven pp.161). Therefore an aim of the current research was to study the personality structure of depressed patients rated with varying levels of TRD. The NEO-FFI was employed as the primary personality measure. The NEO-FFI is one of the most widely used self-rated personality inventories and is comprised of 60-statements rated on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree). There are 12-statements per personality domain ([neuroticism, N; extraversion, E; openness, O; agreeableness, A; conscientiousness, C]). A dimensional score is obtained for each of the five personality domains by summing the 12 items per domain (Costa & McCrae, 1992). There are 28 statements that are reverse scored prior to final summation. Domain scores range from a minimum of 12 to a maximum of 60. The five domains of the NEO-FFI were found to have adequate internal consistency (α = .68 to .86, Costa & McCrae, 1992) and temporal stability (r = .86 to .90, (Robins, Fraley, Roberts, & Trzesniewski, 2001).

Concerns have been raised about the applicability of the NEO-FFI in psychiatric clinical samples as the NEO-FFI was originally developed to be used in healthy populations (Costa & McCrae, 1992). However, recent exploratory structural equation modelling has shown support for the five-factor structure of the NEO-FFI in a large psychiatric clinical sample (N = 1,980), including depressed outpatients, thus providing support for its use in clinical samples (Rosellini & Brown, 2011). The NEO-FFI has been utilised in studies investigating personality pathology, the depression illness course and outcomes of depression (Du et al., 2001; Petersen et al., 2001, Petersen et al., 2002, Rosellini & Brown, 2011; Tang et al., 2009).

An additional concern with using personality inventories in clinical samples, especially depressed samples, is that personality ratings may be influenced by the patients' symptomatic state and may inaccurately reflect the patient's personality (Morey, et al., 2010). In light of this concern, the Collaborative Longitudinal Personality Disorders Study (CLPS) assessed personality structure in 668 depressed inpatients and outpatients using the NEO-PI (the longer version of the NEO-FFI

comprising 240 items), as well as, the presence of DSM-IV Personality Disorders using the Diagnostic Interview for DSM-IV Personality Disorders (schizotypal, borderline, avoidant and obsessive compulsive personality disorder) (Morey et al., 2010). A total of 522 patients (78.1%) were followed for 6-years. Of the 522 patients who participated in the follow-up, 119 (22.8%) met criteria for personality disorder only (no MDD), 241(46.2%) met criteria for MDD and a comorbid personality disorder, and the remaining 73 (14%) patients met criteria for MDD and no comorbid personality disorder at the baseline assessment. At 6-year follow-up, stability of personality traits were similar for personality disorder patients with (N= 241; 46.2%) and without MDD (N = 119; 22.8%) (Morey et al., 2010). This longitudinal study bolsters support for the stability of personality assessments and diagnoses made during a depressive episode and suggest that personality ratings are a valid reflection of personality pathology and not necessarily a state effect due to depressed mood (Morey, et al., 2010).

5.7 Models of Treatment Resistant Depression (TRD) (see Appendix 1).

Treatment information collected from medical records was used to determine the level of lifetime treatment resistance of the participants. It should be noted, that the results reported in Chapters Six and Seven are reliant on participant recall and accuracy of medical chart auditing for information on treatment history. The level of response to past antidepressant trials could not be determined retrospectively. The models of TRD have been used to rate lifetime TRD and as such, all past antidepressant trials were used to rate TRD. It is acknowledged that participants may have responded to medication trials and subsequently relapsed or discontinued medication trials due to side effects or intolerance. Only prospective study designs, which monitor the response and reason for discontinuation, can definitively determine whether or not a trial is a failure. Additionally, the algorithms used to apply the models of TRD to the data, require such minimal treatment trials (e.g. two antidepressant failures) to designate TRD that the inability to capture all past treatment trials does not impede the models' reliability or utility to measure TRD.

The research described in Chapters Six and Seven is cross-sectional and is investigating lifetime not episodic TRD. All participants were admitted to hospital for their depression and were depressed at time of admission as determined by their treating psychiatrist. This suggests that all participants (who were all taking antidepressant medication at time of recruitment) were non-responsive to their current medication trial or had relapsed resulting in admission to hospital. After treatment data were collected, algorithms reflecting the criteria of each TRD model were applied to assess the participants' treatment resistance.

5.7.1 Antidepressant Treatment History Form (ATHF). The ATHF was originally developed to assess the level of antidepressant treatment prior to an individual commencing ECT

(Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012; Oquendo, et al., 2003; Sackeim, Prudic, Devanand, Decina, Kerr, & Malitz, 1990). In the research detailed in Chapter Six and Seven, each past antidepressant trial was independently rated using the ATHF and the separate ATHF trial scores were summed to calculate an overall ATHF score (Oquendo, et al., 2003; Sackeim, Prudic, Devanand, Decina, Kerr, & Malitz, 1990). Longer durations of treatment and optimal doses of antidepressants generated higher trial scores. The total ATHF score is continuous with no pre-defined maximum score.

5.7.2 Thase and Rush Model (TRM). The TRM was the earliest staging model of TRD to be published in the medical scientific literature. This model was developed based on illness staging in other medical specialties such as oncology (Thase & Rush, 1997). Individuals are assigned one of five stages of TRD. The minimum entry requirement to be staged on the TRM is the failure of one antidepressant trial. Participants who had not failed one antidepressant trial were given the score of 0 (i.e. participants who were currently on their first antidepressant medication trial). The TRM does not define the dose and duration of antidepressant trials. The model is also hierarchical, and it assumes that failure of a monoamine oxidase inhibitor (MAOI) is indicative of a higher level of resistance than the failure of a tricyclic antidepressant (TCA). The TRM does not rate augmentation or combination strategies or any additional clinical information such as illness duration or symptom severity.

5.7.3 European Staging Model (ESM). The ESM was developed in 1999 by a European research group in response to the issues raised about the TRM (Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012; Souery, et al., 1999). Individuals are divided into three categories: treatment non-response, TRD and chronic resistant depression (CRD) (Souery, et al., 1999). The distinction between TRD and CRD is arbitrarily chosen. In the ESM model, TRD is defined as the non-response to two adequate antidepressant trials of two different antidepressant classes (treated for 6 to 8 weeks per trial). Chronic resistant depression (CRD) is designated if the patient has been treated for more than 12 months without adequate response. The ESM defines non-response as less than 50% reduction on the HAM-D or the Montgomery-Asberg Depression Rating Scale (MADRS) (Souery, et al., 1999).

It was not possible to determine the extent of any reduction in symptom severity in the current study as treatment history was collected retrospectively. In addition, as this is a cross-sectional study relying on participant recall and accuracy of medical record chart auditing, it was not possible to determine the level of response to past medication trials. It is acknowledged that participants could have responded to previous trials and relapsed at a later date but for the purpose of this study lifetime TRD was measured. The ESM model determines the level of TRD by assessing the length of trial durations. In failed trials, the longer the trial duration the higher the

level of TRD assigned to the individual. Individuals were required to have trial durations greater than 12 months to be assigned to CRD (Souery, et al., 1999).

5.7.4 Massachusetts General Hospital Staging Model (MGHS). The MGHS was published in 2003 and rates TRD on a continuous scale with no pre-defined maximum score (Fava, 2003). The model includes augmentation strategies and ECT. There is no antidepressant hierarchy in the MGHS model; all failed treatment trials are given the same rating (1 point per trial). The weight given to failed ECT course (3 points) compared to a failed antidepressant trial (1 point) is unexplained (Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012).

For the purpose of the current study, 3 points were added if the individuals had received one or more courses of ECT, rather than 3 points per ECT course. This was decided as Ruhe et al. (2012) highlighted that rating many treatment trials might cause methodological problems due to extremely high scores for a small number of patients. Treatment strategies such as optimisation, combination and augmentation trials were considered in the model.

5.7.5 Maudsley Staging Method (MSM). The MSM is the most recent staging model and was developed in 2009 (Fekadu et al., 2009). This model is multidimensional in nature and includes illness duration, symptom severity and treatment strategies such as augmentation and ECT (Fekadu et al., 2009). The MSM provides a continuous score ranging from 3 to 15 (Fekadu et al., 2009; Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012). The MSM also categorises TRD into three categories: mild (scores between 3 and 6), moderate (scores between 7 and 10) and severe (scores between 11 and 15) (Fekadu et al., 2009; Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012). In the current study the dimension of symptom severity was based on current symptom severity, as indicated by the 17-item HAM-D. As the majority of depressed inpatients in the current study reported a chronic presentation (N = 64; 91.4%) without definable wellness periods (two months or more with minimal or no depression symptoms), the duration dimension was assumed to be lifetime duration of illness (acute or chronic) rather than episode duration as intended by the original investigators (Fekadu et al., 2009). The MSM model does not incorporate an antidepressant hierarchy and thus all trials were scored equally regardless of antidepressant class.

5.8 Ethical Considerations

Chapters Six and Seven outlines research conducted on persons with a mental illness. Particular ethical considerations were addressed prior to conducting this research. The recruitment of vulnerable individuals into the research project was considered thoroughly and strategies were put into place to protect these individuals. The treating psychiatrist was involved in the recruitment of participants and was made aware of any adverse emotional or psychological effects of the research. Participants were only recruited with the agreement of the treating psychiatrist. The

research protocol and procedures were reviewed and approved by the University of Queensland Medical Research Ethics Committee (ethics approval number: 2010001485) and the New Farm Clinic Medical Advisory Committee (MAC) (Appendix 3).

Information sheets were given to all participants and included a full description of the research with the risks and benefits clearly detailed. Participants were given sufficient time to consider their participation and were encouraged to discuss participation with their family or friends. The participants' right to withdraw from the study at any time was highlighted in the information sheet and also orally throughout the interview.

The privacy and confidentiality of the participants was protected at all times. De-identified data were collected and stored to ensure the privacy and confidentiality of all participants. The privacy of participants would only be breached if the disclosure of information during the interview risked the safety of the individual or other parties.

Chapter Six

The degree of treatment resistant depression (TRD) in a tertiary care setting

6.1 Introduction

In this chapter the primary data collected on the depressed inpatient sample are reported with a particular emphasis on the socio-demographics, clinical features and treatment history of the sample. Many of the reported correlates of TRD have not been consistently replicated in the medical scientific literature due to differing research methodologies and the use of varying definitions of TRD. Previous research has investigated the correlates of non-response in MDD but a limited number of studies have investigated the correlates of TRD using standardised definitions. The assessment of TRD using multiple models and definitions allowed for more comprehensive investigation of the correlates of TRD. It also allowed for an assessment of the relatedness between the models and whether the widely used definition of the failure of two antidepressants is comparable to more complex staging models in terms of its predictive utility.

A major criticism of using the failure of two antidepressants to define TRD, is that it is too broad to effectively conceptualise TRD in research and clinical practice. The existing more complex models of TRD were developed to rate TRD on a continuum of resistance rather than a dichotomous assessment of resistance based simply on antidepressant failures. However, these models were developed without apparent reference to empirical data and without an empirically supported theoretical background. Thus the research outlined in this thesis provides a unique opportunity to assess and cross-validate the current definitions and models of TRD using a sample of depressed inpatients with a long-standing history of depression and the use of multiple treatment modalities. The analysis for this chapter was designed to address the following research questions:

RQ4. What is the degree of treatment resistance in a sample of depressed inpatients?

RQ5. What factors predict TRD using a composite index of TRD compared to the definition of the failure of three or more antidepressants?

Firstly, this chapter provides an overview of current knowledge of TRD and the known correlates associated with treatment resistance. This background was required in order to gain a comprehensive understanding of the concept of TRD and to provide support for the entry of particular variables into the predictive models of TRD. The results section of this chapter begins by describing the inpatient sample. The socio-demographic characteristics, clinical features and treatment history of the sample are detailed, highlighting the complex and highly chronic nature of

the sample. The degree of treatment resistance in the sample is determined by reporting the mean scores of the five models of TRD and the percentage of the sample who meet criteria for treatment resistance using the failure of three or more antidepressants. The five models of TRD and the definition of the failure of three or more antidepressant trials are assessed for relatedness and whether they rate TRD in a similar way. A composite index of TRD combining the scores from the five existing models of treatment resistance is proposed in order to investigate the correlates of TRD in the inpatient sample across all models. Two regression models are performed with two different outcome variables. Model 1 uses the TRD composite index as the outcome variable and Model 2 uses the failure of three or more antidepressants as the outcome variable. The models are compared to determine whether rating TRD on a continuum using staging models compared to rating TRD dichotomously, as the failure of three or more antidepressants, provides more predictive utility. The correlates of TRD revealed by each model are compared and discussed.

6.2 Background

Treatment-resistant depression (TRD) is the conventional term for non-response to treatment in individuals with Major Depression. The STAR*D study, a large multisite open-label trial of treatments for depression, found that 67.7% of individuals failed to respond to four sequential antidepressant trials (Rush, 2007; Warden et al., 2007). STAR*D also found that as the number of treatment strategies trialled in non-responders increased the probability of response and remission diminished (Rush, 2007; Warden et al., 2007). These STAR*D findings resulted in a call for more vigorous treatment trials to potentiate the benefit of early treatment (Warden et al., 2007). The exact prevalence of TRD is difficult to estimate due to major variations in research methodology and lack of a standardised or universally adopted definition of TRD (Nemeroff, 2007). Previous studies investigating the factors associated with treatment resistance have not been consistently replicated and are limited by research and sample heterogeneity.

The underlying aetiology of depression has been widely studied with many different theories proposed. Applying these theories to a unified aetiological model of depression has been difficult, as only selected theories apply to certain types of depression and to particular points across the illness course (Hasler, 2010). In addition, the DSM-IV and DSM-5 are atheoretical as to the cause of depression (American Psychiatric Association, 2000). Pathophysiological theories of depression include genetic vulnerability, altered hypothalamic-pituitary-adrenal (HPA) axis activity, deficiency of monoamine neurotransmitters, dysfunctional brain regions, neurotoxic and neurotrophic processes, reduced activity of gamma amino butyric acid (GABA), dysregulation of the glutamate system and impaired circadian rhythms (Hasler, 2010). Cognitive and behavioural theories of depression postulate that the development and maintenance of depression is the result of stress,

learned helplessness, negative attributions and/or maladaptive cognitive structures. The applicability of these theories to treatment response in depression is not yet clearly understood.

Misdiagnosis, individual clinician differences, co-morbidity, inadequate treatment and patient heterogeneity are all considered to contribute to treatment resistance. However, these contributing factors are most likely associated with the phenomenon of pseudoresistance. Pseudoresistance refers to treatment resistance as a result of diagnostic and/or treatment factors. Thus, misdiagnosis and inadequate treatment can be misconstrued as treatment resistance when they more appropriately lead to pseudoresistance. Several staging models have been developed to identify and rate patients with varying levels of TRD. Many of the models screen for inadequate treatment by only including treatment trials that have met pre-established criteria of adequacy. Despite their potential utility, the available staging models of TRD are scarcely used in research and clinical practice, with many employing instead the simpler construct of the failure of two antidepressants as their chosen definition of treatment resistance (Petersen, et al., 2005).

The economic costs associated with depression, particularly TRD, are high. The greater the degree of treatment resistance, as measured by the number of medication changes a patient receives, the greater the associated health care expenditures (Olchanski et al., 2013; Russell et al., 2004). Higher costs for imaging tests, physician visits and psychiatric hospitalisations account for higher direct healthcare expenditures for TRD patients (Fostick et al., 2010). Additionally, individuals with TRD have a higher rate of working days lost compared to depressed individuals who respond to treatment (Fostick et al., 2010). This indirect cost of reduced work productivity is particularly important when considering the global economic and disability burden associated with depression (Lepine & Briley, 2011). The high economic and disability burden posed by TRD together with the ambiguity surrounding the phenomenon makes the identification of risk and predictive factors imperative. The elucidation of differences between those who respond to treatment and those who do not respond to treatment should help to identify potential risk factors for TRD and perhaps contribute to the development of a panoptic model of treatment resistance.

6.2.1 Biological correlates. The biological bases of Major Depressive Disorder (MDD) and any neurobiological differences that might exist between treatment responsive and treatment-resistant depression remain unclear. This section outlines the reported differences in brain structure and function, as well as molecular differences in TRD patients in comparison to healthy controls and non-resistant depressed patients.

6.2.1.1 Neuroendocrine and immune systems. Depression has been considered to be a disorder of immune suppression and immune activation (Blume, Douglas & Evans, 2011). A bidirectional relationship between inflammation and depression is thought to exist (Han & Yu, 2014). Particular attention has been given to cytokines, cell signalling proteins that mediate and

regulate immune response and depression (Han & Yu, 2014). Pro-inflammatory cytokines promote the inflammatory response whilst anti-inflammatory cytokines work to reduce inflammation and initiate healing (Han & Yu, 2014). Efforts to identify neuroendocrine and immune dysfunction in depression have focused on alterations in hypothalamic-pituitary adrenal (HPA) regulation and other neuroendocrine changes such as elevated cortisol levels as well as altered immune function (Pariante & Lightman, 2008; Hasler, 2010).

Hyperactivity of the HPA axis is thought to be activated by the proliferation of inflammatory cytokines (Han & Yu, 2014). An increase in pro-inflammatory cytokines has been associated with HPA axis disturbance and is thought to lead to the release of the stress-hormone, cortisol (Han & Yu, 2014). Cortisol has a long standing association with depression with cortisol reported to be elevated in depressed patients (Han & Yu, 2014). Furthermore, over-activity of the HPA axis in depression is supported by findings which suggest chronic imipramine treatment (tricyclic antidepressant) down-regulates the plasma levels of important hormones involved in the HPA axis thus highlighting the role of the HPA axis in depression and immune dysfunction (Bauer, et al., 2003; Han & Yu, 2014).

In studies comparing treatment resistant samples to controls, HPA axis disturbance (Carvalho, et al., 2013), proliferative activity of T cells (Kubera, Basta-Kaim, Wrobel, Maes, & Dudek, 2004) and overall activation of the inflammatory system (Carvalho, et al., 2013; Kubera, Basta-Kaim, Wrobel, Maes, & Dudek, 2004) have been associated with TRD. However, elevated basal cortisol levels have not been reported in TRD inpatients (N = 36) in comparison to healthy controls (N = 31) (Bauer, et al., 2003). Despite the unexpected lack of reported increases in basal cortisol in TRD patients, inpatients with TRD have shown altered immuno-neuroendocrine regulation due to glucocorticoid-induced suppression of lymphocyte proliferation (e.g. T cells) in comparison to the healthy controls (Bauer, et al., 2003). This finding suggest that immune function and steroid regulation in TRD patients may be associated with lymphocyte steroid resistance rather than elevated levels of cortisol as previously reported in depression (Bauer, et al., 2003).

As highlighted in section *1.6.6 Biological models*, treatments for depression can help elucidate the role specific biological correlates might play in depression. Coenzyme Q10 (CoQ10), which is synthesised from the amino acid tyrosine is hypothesised to have anti-inflammatory effects and has been studied as a potential treatment for TRD (Maes, Mihaylova, Kubera, Uytterhoeven, Vrydags, & Bosmans, 2009b). Low CoQ10 levels in depression may indicate a greater inflammatory response (Maes, Mihaylova, Kubera, Uytterhoeven, Vrydags, & Bosmans, 2009b). In line with previous findings, which associate TRD with greater activation of the inflammatory system, lower plasma CoQ10 has been linked to TRD and also to individuals with depression and co-morbid chronic fatigue syndrome (Maes, Mihaylova, Kubera, Uytterhoeven, Vrydags, &

Bosmans, 2009b). Thus, CoQ10 supplementation may conceivably provide benefit as an adjunct to treatment for resistant depression (Maes, Mihaylova, Kubera, Uytterhoeven, Vrydags, & Bosmans, 2009b). However, to date, no randomised controlled trials have been conducted to confirm the efficacy of CoQ10 as treatment for depression.

6.2.1.2 Neural systems and circuits. Atrophy in particular brain regions and structures have been associated with depression. Reduced hippocampal volume has repeatedly been linked to depression and may be the result of prolonged exposure to glucocorticoids, HPA axis disturbance and/or stress-induced reductions in neurotrophic factors (Sheline, 2011). Furthermore, a small hippocampal volume may be a risk factor for depression and treatment resistance (Sheline, 2011). The entorhinal cortex has reciprocal connectivity with the hippocampus and has not been as widely studied in depression (Furtado, Maller, & Fitzgerald, 2008). In terms of treatment response, female TRD outpatients (N = 15) were found to have significantly smaller entorhinal cortex volumes in comparison to female age and gender matched healthy controls (N = 17) (Furtado, Maller, & Fitzgerald, 2008). The same result was not found for males (Furtado, Maller, & Fitzgerald, 2008). Females maybe more affected by depression-related atrophy of the entorhinal cortex than males (Furtado, Maller, & Fitzgerald, 2008).

Neural circuitry within specific neural systems mediates stress responsiveness, mood and emotional regulation (Ressler & Mayberg, 2007). Neuroimaging techniques have been used to identify dysfunctional circuits in patients with TRD. In particular, the use of a perfusion magnetic resonance imaging (MRI) technique known as arterial spin labelling (ASL) has found hyperfusion regions in the bilateral subgenual anterior cingulate cortex (sACC), left dorsomedial prefrontal cortex and left subcortical areas (putamen, pallidum and amygdala) in TRD patients compared to healthy controls (Duhameau, et al., 2010). Hyperactivation of the sACC has provided evidence for dysfunctional cortico circuits in depression (Duhameau, et al., 2010). The subgenual cingulate region has been previously implicated in modulating negative mood states and also in antidepressant treatment response (Seminowicz, et al., 2004).

The limbic-cortical-striatal-pallidal-thalamic circuit may also be implicated in TRD as evidenced by lower magnetization transfer ratios in certain right hemisphere limbic and striatal regions in TRD patients compared to healthy controls (Zhang, et al., 2009). This circuit closely resembles the default-mode network. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) neuroimaging techniques have revealed the default-mode network, a system of brain regions (medial prefrontal cortex, posterior cingulate/ retrosplenial cortex and left and right inferior parietal lobules) that show decreased activation during goal-orientated or attention-demanding tasks (Whitfield-Gabrieli & Ford, 2012). The default-mode network is associated with episodic memory, self-reflection and emotional regulation (Drevets, Price, & Furey,

2008; Ma, et al., 2012).

A recent study has used voxel-based morphometry of structural and fMRI data to compare the concentrations of grey matter in the default-mode network regions between TRD (N = 18), treatment responsive depression (N = 17) and healthy controls (N = 17) (Ma, et al., 2012). Resting-state functional connectivity analysis was also conducted to investigate the grey matter abnormalities between the groups (Ma, et al., 2012). Both the TRD and treatment responsive depression groups showed significant grey matter abnormalities in the right middle temporal cortex and bilateral caudate. In the right middle temporal cortex and bilateral caudate, patterns of resting-state functional connectivity were different between the TRD, treatment responsive depression and healthy controls (Ma, et al., 2012). Alterations in functional connectivity in different brain regions between TRD and treatment responsive patients were found. In particular, the regions of aberrant connectivity were mainly located in the default-mode-network (Ma, et al., 2012). This finding provides evidence for the default-mode network's likely involvement in the pathophysiology of depression (Ma, et al., 2012). Due to only subtle differences in functional connectivity between TRD and treatment responsive patients, the study does not clearly depict the involvement of the default-mode-network on treatment response.

A second study used structural MRI, voxel-based morphometery and multivariate pattern analysis in an attempt to classify TRD patients (N = 18), patients with first-episode MDD (N = 17) and healthy controls (N = 17) (Liu, et al., 2012). Differing patterns of grey matter and white matter volumes in the areas of the brain regions associated with the default-mode network significantly discriminated between TRD patients, patients with first-episode MDD and healthy controls (Liu, et al., 2012). Therefore, sensitive neuroimaging methods may have greater utility in identifying subtle alterations in the default-mode network associated with treatment response (Liu, et al., 2012).

The prefrontal-amygdala-pallidostrial-mediothalamic circuit is another dysfunctional neuroanatomic circuit which has been linked to mood regulation and treatment response in individuals with MDD (Guo, et al., 2011). Aberrations in the prefrontal-amygdala-pallidostrial-mediothalamic circuit characterised by abnormal regional homogeneity in several brain regions have been associated with TRD (N = 24) in comparison to healthy controls (N = 19) (Guo, et al., 2011). A resting-state fMRI study using a regional homogeneity technique found that TRD was associated with abnormal brain activity in the regions linked to the prefrontal-amygdala-pallidostrial-mediothalamic circuit and also in many cerebellum regions (Guo, et al., 2011).

6.2.1.3 Neurophysiological activity. Abnormal neural activity in specific brain regions could be a neurophysiological marker for TRD. Previous studies have linked reduced medial prefrontal and hippocampal activity to TRD (Kumari, et al., 2003). The hippocampus has been studied extensively in relation to the aetiology of depression. Using fMRI, one study proposed that

individuals with TRD have abnormalities in processing and attaching meaning to positive events as shown by reduced response in the medial frontal gyri and hippocampi to emotion evoking stimuli (Kumari, et al., 2003).

Abnormal brain electrophysiological recordings have been suggested to result from dysfunctional neurotransmitters and could be a neurophysiological marker of TRD (He, et al., 2010a). Mismatch negativity, an early component of cortical event-related potentials (ERPs), is recorded during an oddball task (the presence of an odd stimulus amongst a sequence of stimuli) and may indicate information processing impairments (He, et al., 2010a). Generated in the supratemporal area and frontal lobe, mismatch negativity is mediated by neurotransmitters associated with depression, such as dopamine, serotonin, glutamate and GABA (He, et al., 2010a). High mismatch negativity amplitudes in TRD indicate a lack of inhibition of the response to the irrelevant stimuli or increased cortical neuronal excitability in the frontal lobe and could be related to dysfunctional neurotransmitter systems (He, et al., 2010a).

6.2.1.4 Neurotransmitter dysfunction. Theories of neurotransmitter dysfunction in depression are well established. The predominant theory hypothesises that depression is related to decreased availability of monoamine neurotransmitters (see section **1.6.6 Biological models**). Noradrenaline and serotonin have most commonly been implicated in depression (Mulinari, 2012). In more recent times the monoamine theory of depression has shifted from a theory of decreased levels of the main monoamines (particularly noradrenaline and serotonin) to a theory of neurotransmitter dysfunction resulting from an interaction between stressful life events and the serotonin transporter gene (Caspi et al., 2003; Mulinari, 2012). A gene-by-environment interaction is theorised where a functional polymorphism of the serotonin transporter gene moderates the influence of stressful life events in people with depression (Caspi et al., 2003). However, a recent meta-analysis comprised of 14 studies found no evidence of the serotonin transporter gene interacting with stressful life events to increase the risk of depression in either males and females (Risch et al., 2009).

Current antidepressants act on multiple monoamine neurotransmitters and have targeted effects on neurotransmitter function (Mulinari, 2012). However, the response to these conventional antidepressants is delayed and often unsatisfactory (Kugaya & Sanacora, 2005; Mulinari, 2012). The poor response to antidepressants has led to suggestions that the monoamine theory of depression does not fully explain neurotransmitter dysfunction in depression and other neurotransmitters and systems may contribute to the dysfunction (Kugaya & Sanacora, 2005). In particular the glutamatergic system has garnered significant attention (Kugaya & Sanacora, 2005).

Gamma-amino-butyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system and balances neuronal excitability produced by glutamate (Kugaya & Sanacora,

2005). The efficacy of antiglutamatergic agents (such as lamotrigine) for the treatment of depression provides support for excessive glutamate induced excitation in depression (Kugaya & Sanacora, 2005). In relation to treatment resistance, lower levels of GABA in the occipital cortex have been found in medication-free TRD outpatients (N = 15) in comparison to healthy controls (N = 24) and medication free treatment responsive depression outpatients (N = 18) (Price, et al., 2009). Furthermore, deficits in $GABA_A$ and $GABA_B$ receptor-mediated inhibitory neurotransmission distinguished TRD (N = 25) from healthy controls (N = 25), medicated previously depressed patients (N = 19) and un-medicated currently depressed patients (N = 16) (Levinson, Fitzgerald, Favalli, Blumberger, Daigle, & Daskalakis, 2010). Therefore, marked GABAergic deficits may be characteristic of TRD, suggesting the possible usefulness of therapeutic strategies aimed at potentiating cortical GABA in patients with TRD (e.g. lamotrigine augmentation, electroconvulsive therapy and transcranial magnetic stimulation) (Levinson, Fitzgerald, Favalli, Blumberger, Daigle, & Daskalakis, 2010).

6.2.2 Genetic Correlates. Advances in genetic epidemiology have spurred research investigating the role genetics play in the pathophysiology of depression. Researchers have studied the genetics of the serotonin transporter (5-HTT) located on the presynaptic neuron as a way to investigate the serotonergic system (Kishida, Aklillu, Kawanishi, Bertilsson, & Agren, 2007). As many antidepressants target serotonin reuptake mechanisms, the serotonin transporter is a popular site to study the role genetics play in treatment response. Response to treatment in depression is considered to be associated with signalling through 5-HT1A receptor, and with neurogenesis in the hippocampus (Anttila, et al., 2007). Differences in response to treatment have been linked to polymorphisms in the 5-HTT promoter region (5HTTLPR) (Bonvicini, et al., 2010). In particular, less active serotonin transporter alleles may be linked to TRD (Bonvicini, et al., 2010). Brain-derived neurotrophic factor (BDNF) genes have also been implicated in treatment response and the combination of particular BDNF genes and polymorphisms in the 5-HTIA gene are associated with higher risk of TRD (Anttila, et al., 2007). In addition, interactions of BDNF (rs6265) gene polymorphism with its high-affinity receptor, NTRK2 (rs1387923, rs2769605 and rs1565445) gene polymorphisms have also been associated with TRD (Li, et al., 2013). In contrast, polymorphisms of the CREB1 and MAPK1 genes, which are involved in neuroplasticity and inflammatory processes, have not been associated with TRD (Calati, et al., 2013). The presence of particular environmental factors, together with a specific expression of genes, may leave individuals vulnerable to depression and poorer treatment response.

6.2.3 Psychological and Psychosocial Correlates. Although relatively few studies have examined the psychological and psychosocial factors associated with TRD, treatment resistance in depression has been linked to an earlier age of onset (Dudek, et al., 2010; Souery, et al., 2007),

more frequent (Dudek, et al., 2010; Sagud, et al., 2013) and recurrent (Souery, et al., 2007) episodes of depression, longer duration of illness (Sagud, et al., 2013), greater severity of depression (Souery, et al., 2007) and an older current age (Sagud, et al., 2013). Patients with TRD are also more likely to be hospitalised for treatment (Souery, et al., 2007) and to have a greater risk of suicide (Sagud, et al., 2013; Souery, et al., 2007; Pfeiffer, Kim, Ganoczy, Zivin & Valenstein, 2013). Non-remission or partial remission after a previous depressive episode (Dudek, et al., 2010) and non-response to the first antidepressant ever trialled (Souery, et al., 2007) have also been identified as potential risk factors for TRD.

One study used principal component analysis to identify the factor structure underlying the symptom profile of TRD outpatients (N = 260) (Andreasson, et al., 2010). The symptom profile of TRD outpatients was characterised by depressed mood, anxious mood, suicidal thoughts, decreased sleep, concentration difficulties and anhedonia (Andreasson, et al., 2010). A second study (Maes, 2009a) also identified a factor structure characteristic of depressed outpatients (N = 103) rated with TRD on the Thase and Rush staging model (Thase & Rush, 1997). Outpatients with TRD showed concentration difficulties, failing memory, irritability, sadness, sleep disturbances, autonomic disturbances and a subjective experience of infection (self-reported symptoms) (Maes, 2009a). Moreover, a higher prevalence of the "melancholia" subtype of Major Depression has been reported in TRD outpatients (Souery, et al., 2007; Malhi, Parker, Crawford, Wilhelm, & Mitchell, 2005). The melancholia subtype has historically been distinguishable from other types of depression by disturbances in affect, which are disproportionate or without cause, psychomotor retardation, cognitive impairment and vegetative dysfunction (Parker, et al., 2010). Depressed patients classified with the melancholic subtype are less likely to respond to placebos and psychotherapies (Brown, 2007) and are more responsive to tricyclic antidepressants (Perry, 1996) and ECT (Petrides, et al., 2001).

Higher rates of both psychiatric and general medical co-morbid disorders have been reported in association with TRD (Souery, et al., 2007; Amital, et al., 2013). Increased morbidity in TRD patients in selected co-morbid diseases (breast cancer, migraine and glaucoma) have been reported (Amital, et al., 2013). In terms of psychiatric co-morbidity, TRD has been associated with a higher prevalence of co-morbid anxiety disorders (Souery, et al., 2007), panic disorder (Souery, et al., 2007), social phobia (Souery, et al., 2007; Crawford, Parker, Malhi, Mitchell, Wilhelm, & Proudfoot, 2007) and personality disorders (Souery, et al., 2007). TRD has also been linked to a possible bipolar diathesis as evidenced by higher scores on the Mood Disorder Questionnaire (MDQ) (Dudek, et al., 2010; Kiejna, et al., 2010) and Hypomania Checklist (HCL-32) (Dudek, et al., 2010). However, the presence of high levels of bipolarity symptoms in TRD samples could be due to the presence of antidepressant-induced hypomania. A retrospective chart audit of 146 TRD

patients, found evidence of treatment induced hypomania or hypomanic-like episodes in a small number of TRD audited cases (N = 16) (Bader & Dunner, 2007). The link between bipolarity and TRD raises the possibility of pseudoresistance due to misdiagnosis. However, these studies report bipolarity features not proof of co-morbid bipolar disorders. Subclinical bipolarity features or treatment induced hypomania rather than bipolar co-morbidity may be associated with TRD.

Patients with TRD are reported to experience a higher number of stressful life events, including immigration, death of a family member, interpersonal relationship problems, job loss, financial stress, severe health conditions, and life threatening situations (Amital, et al., 2013). In a recent study, adverse childhood experiences including trauma and bullying were reported as common in TRD (defined as the failure of one antidepressant) with 62% of TRD inpatients (N = 137) reporting childhood adversity (Tunnard et al., 2014). In the TRD sample, a poorer clinical course, earlier age of onset, episode persistence and recurrence was associated with childhood adversity (Tunnard et al., 2014). Childhood adversity was also predictive of lifetime suicide attempts in the TRD sample (Tunnard et al., 2014). An early study which used the Thase and Rush (1997) model of TRD to define treatment resistance reported high levels of trauma and emotional abuse in TRD patients compared to non-TRD patients (Kaplan & Klientob, 2000). The authors conclude that early trauma may result in an increased vulnerability to life stressors in patients with TRD (Kaplan & Klientob, 2000). As Caspi et al. (2003) hypothesised, there may be an interaction between stressful life events and the development of depression which is moderated by polymorphisms of the serotonin transporter gene. Individuals with one or two copies of the short allele of the serotonin transporter (5-HTT) gene may be more vulnerable to developing depression after experiencing a stressful life event compared to individuals with the long allele of the 5-HTT gene (Caspi et al., 2003). These individuals may also have a poorer response to treatment, as well as an increased vulnerability to depression after stressful life events (Serretti et al., 2007).

Kaplan and Klientob (2000) also reported poorer occupational functioning with 40% of the sample currently receiving disability pensions for their depression. Poorer occupational functioning as evidenced by a higher prevalence of job loss (Amital, et al., 2013) and mild to moderate impairment in work-related activities (Petersen, et al., 2004) is common in TRD samples. TRD patients have been reported to have good to fair interpersonal relations, a poor level of involvement in recreational activities, and mild impairment in their enjoyment of sexual activity (Petersen, et al., 2004).

Both TRD outpatients and clinicians have rated the social adjustment of patients as poor (Petersen, et al., 2004). Furthermore, higher social inhibition and lower perceived social support have been found in TRD patients (Crawford, Parker, Malhi, Mitchell, Wilhelm, & Proudfoot, 2007). Low scores on the sociability trait of the Zuckerman-Kuhlman Personality Questionnaire have been

reported in TRD samples (He, Chai, Zhang, Yu, Chen, & Wang, 2010b). It has been suggested that socially inhibited individuals may not be able to create and maintain the social networks needed to provide protective support against moderate life stress and depression (Crawford, Parker, Malhi, Mitchell, Wilhelm, & Proudfoot, 2007).

The processing of anger, happiness and sadness is delayed in TRD patients, indicating a dysfunction in emotion-related attention (He, et al., 2012). The recognition and interpretation of facial expression is extremely important for interpersonal relationships and social engagement. Deficits in processing facial emotions may influence the attention and recognition given to a particular emotion and, as a result, negatively impact upon interpersonal relationships and social functioning in TRD.

A recent study has investigated the association between cognitive functioning, depression symptoms and psychosocial functioning in a sample of outpatients with TRD (N = 33) (Gupta, et al., 2013). Impairment in real-world behaviour domains (work, interpersonal relations, satisfaction and recreation) in TRD was associated with more severe depression symptoms (Gupta, et al., 2013). Greater impairment in the recreation domain was associated with poorer sustained attention (Gupta, et al., 2013). Additionally, patients with TRD were shown to have mildly reduced performance across all neurocognitive domains, including sustained attention, verbal learning, verbal working memory, information processing speed, verbal fluency and executive functioning (Gupta, et al., 2013). It has been proposed that impaired cognitive impairments and poor functioning in TRD may be mediated by poor motivation, dysfunctional attitudes or stigma that may inversely affect competence and performance on particular tasks (Gupta, et al., 2013).

6.2.4 Identifying TRD in clinical practice. The above section has canvassed current understanding of TRD and highlighted the need for future research. Heterogeneity in TRD research has led to little progress in furthering our understanding of this phenomenon and has impeded the development of standardised practices to appropriately treat individuals with resistant depression. As discussed in depth in Chapter Two, several staging models of TRD have been developed to categorise levels of treatment resistance. These models have evolved over time from simply rating the adequacy of a single treatment trial (Antidepressant Treatment History Form; ATHF) (Oquendo, et al., 2003; Sackeim, Prudic, Devanand, Decina, Kerr, & Malitz, 1990) to a multi-dimensional staging model incorporating illness duration, symptom severity and treatment strategies (Maudsley Staging Method; MSM) (Fekadu et al., 2009).

A recent systematic review acknowledged that the available staging models had not been validated properly (Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012) and the five models had not been evaluated against one another in the same study. An earlier study tested the validity of two of the available models of TRD (Petersen, et al., 2005). The Thase and Rush Model (TRM) (Thase

& Rush, 1997) and the Massachusetts General Hospital Staging method (MGHS) (Fava, 2003) were found to be highly correlated with one another but the MGHS demonstrated significantly greater ability to predict non-remission in individuals with MDD (N = 115) who were treated and assessed at academic specialty clinics over a 3-year period (Petersen, et al., 2005).

6.2.5 Hypotheses

RQ4. What is the degree of treatment resistance in a sample of depressed inpatients?

As noted earlier in this thesis (see Chapter Four, pp 107), community-residing individuals who reported a history of inpatient and outpatient treatment for depression exhibited more chronic and complex depressive illnesses than individuals who reported a history of outpatient treatment alone or who reported a history of no treatment for their depression. In addition, the literature indicates that patients with TRD are more likely to be hospitalised (Sourey et al., 2007) and have higher health service utilisation rates and higher healthcare costs than patients with treatment responsive depression (Russell et al., 2004; Olchanski et al., 2013). Therefore it is hypothesised that there will be a moderate to high level of TRD in the inpatient sample.

RQ5. What factors predict TRD using a composite index of TRD compared to the definition of the failure of three or more antidepressants?

In line with Petersen et al. (2005) who empirically validated two of the existing models of TRD (the TRM and MGHS) and found them to be highly correlated, it is anticipated that all five existing models will be interrelated and highly correlated to one another. If there is a high level of relatedness between the models this will suggest that they rate TRD in similar way or that they measure the same underlying construct. In this case, it makes sense to combine the models to produce a single composite index.

It is hypothesised that a composite index of TRD will be a superior measure of treatment resistance when compared to the dichotomous definition of the failure of three or more antidepressants. An exploratory analysis is proposed to investigate the factors associated with TRD as previous research has inconsistently reported associations between clinical features, socio-demographic characteristics and TRD. As such, no specific hypotheses have been defined.

6.3 Methods

6.3.1 Methodology and measures. The research methodology for the resulted below, including the study design, recruitment and measures, have been detailed in Chapter Five.

6.3.2 Statistical analysis. All statistical analyses were performed in Stata 12 (StataCorp LP, 2011). Mann-Whitney U tests and Chi-square tests were used to assess differences between group means in the inpatient sample. Ordinary Least Squares regression (OLS) and logistic regression were used to determine which variables were significantly associated with TRD. Pairwise Pearson

product-moment correlations were performed to assess the relationship between the five models of TRD. Figure 6.1 is a matrix displaying the pairwise correlations between the five models. Figure 6.2 displays the variability of each TRD model and the TRD index. Figures 6.1 and 6.2 were created in Stata 12 using the downloaded programs PLOTMATRIX (Mander, 2004) and STRIPPPLOT (Cox, 2003) respectively.

6.3.3 TRD index. An index of TRD was developed based on the five available published models of TRD (see Appendix 1). In brief, the individual model scores were standardised using z-scores and for each inpatient participant the five model z-scores were summed to create a TRD index score. The TRD index was used as the dependent variable in a series of OLS regression models.

The models of TRD have not been universally adopted for use in research and clinical practice and there is no consensus on which model is superior at assessing TRD. Additionally there is limited empirical data to support one model over the other. The development of a composite TRD index provides the opportunity to cross-validate the models by examining the concurrent validity between models. This approach also allows for examination the construct of TRD without constricting the findings to one atheoretical model of TRD. The benefit of employing a TRD index is that degree of TRD is not dependent on how an individual model defines TRD rather it considers how each model defines TRD.

6.4 Results

6.4.1 Socio-demographic characteristics. Table 6.1 displays an overview of the socio-demographic characteristics of the inpatient sample. As expected in depression studies, the majority of the inpatient sample were female (N = 51; 72.9%) and the mean age at time of interview was 42 years (SD = 14.2; range 19-70). At the time of assessment, 40.0% (N = 28) of the sample were married or in a de facto (common law) relationship, 32.9% (N = 23) of the sample were divorced or separated, and the remaining 27.1% (N = 19) of the sample were single. The majority of the inpatient sample had a high school or trade education (N = 47; 67.1%) with the remaining inpatients in the sample having a tertiary level education (N = 23; 32.9%). Over half the inpatients (N = 37; 52.9%) were unemployed and 15.7% (N = 11) of inpatients were retired or not in the workforce. Only 31.4% (N =22) of the sample were employed at time of assessment and over half of the sample were financially supported by a disability pension as their main source of income (N = 34; 48.6%). Other sample characteristics such as reported sexual orientation and remoteness of permanent place of living are displayed in Table 6.1.

6.4.2 Clinical features. All 70 participants met diagnostic criteria for current DSM-IV MDD during the current hospital admission. At time of assessment the inpatient sample endorsed

on average seven out of nine DSM-IV MDD diagnostic criteria (*M* = 7.2; *SD* = 1.1) and had a mean 17-item Hamilton Depression Rating Scale score of 23.5 (*SD* = 5.3; range 11 to 38) indicating a moderate level of depression severity in the sample. On the self-reported Kessler Psychological Distress Scale (K-10) the sample had on average a very high level of current psychological distress (*M* = 35.3; *SD* = 4.9). See Table 6.2.

Participants were asked to report the age they first experienced an episode of depression, defined as a period of two weeks or more when they had symptoms of depression most of the day nearly every day. The self-reported average age of onset in the sample was 25.2 years (*SD* = 13.1; range 9-63). For some participants who experienced childhood adversity or trauma the age of onset was as young as 9 years old. When asked to report how many episodes of depression they had experienced during their lifetime the majority of participants (*N* = 59; 84.3%) had an indefinable number of lifetime episodes without significant periods of wellness (defined as a two month period with no or minimal symptoms of depression) since onset. These participants reported having experienced too many episodes to count and/or constant low mood since the onset of the depressive disorder. Thus, these individuals had chronic (DSM-IV) or persistent (DSM-5) depression, or so-called "double depression" (DSM-IV MDD plus Dysthymic disorder). The remaining participants (*N* = 11, 15.7%) reported definable episodes of depression with a mean number of lifetime episodes of 2.5 (*SD* = 1.4). The average lifetime depression illness duration (calculated by subtracting age of onset from age at time of assessment) was 16.8 years (SD = 11.44) ranging from 1 to 48 years.

Unsurprisingly, given the high number of participants who were unable to identify a distinct number of lifetime episodes of depression, the majority of the sample had a chronic depression illness duration defined as a duration greater than two years (N = 64; 91.4%). Participants with current chronic depression (N = 64; 91.4%) were more likely to have reported an indefinable number of lifetime episodes of depression compared to participants with non-chronic current depression (N = 6; 8.6%), χ^2 (1) = 12.86, $p < .001$ (see Table 6.2).

Table 6.1
Socio-demographic characteristics of the inpatient sample

Socio-demographic characteristic	N (%)/ Mean ± SD (range)
Gender	
Female	51 (72.86)
Male	19 (27.14)
Age (years)	42 ± 14.18 (19 to 70)
Sexual orientation	
Heterosexual	67 (95.71)
Homosexual	3 (4.29)
Martial Status	
Married/de facto	28 (40)
Divorced/separated	23 (32.9)
Never married	19 (27.1)
Widowed	0
Education	
High school/skilled vocation	47 (67.14)
Tertiary	23 (32.86)
Employment Status	
Employed	22 (31.4)
Unemployed	37 (52.9)
Retired/not in workforce	11 (15.7)
Main income source	
Disability pension	34 (48.57)
Employment	13 (18.57)
Spouse income	10 (14.29)
Income protection	2 (2.86)
Service pension e.g. police, veteran	5 (7.14)
Other government pension e.g. new start, aged, carer	4 (5.71)
Other source e.g. divorce settlement, superannuation	2 (2.86)
Remoteness based on postcode	
Major city	54 (77.14)
Inner regional	10 (14.28)
Outer regional	6 (8.57)
Remote	0
Very remote	0

Note. Remoteness was determined using the Australian Bureau of Statistics and Australian Government Department of Health remoteness area tool (2006)

Table 6.2
Clinical features of the inpatient sample

Clinical feature	N (%)/ Mean ± SD (range)
Age of onset (years)	25.17 ± 13.09 (9 to 63)
Chronicity	
Non-chronic (< 24 months)	6 (8.57)
Chronic (> 24 months)	64 (91.43)
Episodes of depression	
Indefinable (no distinct number of episodes)	59 (84.29)
Definable (distinct number of episodes)	11 (15.71)
Number of episodes in those with definable episodes	2.45 ± 1.44 (1 to 5)
History of suicide attempt	
Yes	41 (58.57)
No	29 (41.43)
Number of lifetime suicide attempts	.94 ± 1.03 (0 to 3)
History of deliberate self harm	
Yes	29 (41.43)
No	41 (58.57)
History of childhood sexual abuse	
Yes	22 (31.43)
No	48 (68.57)
Number of first generation family members with depression	.77 ± .94
0	36 (51.43)
1	18 (25.71)
2	12 (17.14)
3	4 (5.71)
Family history of suicide	
Yes	10 (14.29)
No	60 (85.71)
Number of endorsed DSM-IV MDD criteria	7.16 ± 1.14 (5 to 9)
Kessler Psychological Distress Scale (K-10) score	35.34 ± 4.87 (19 to 44)
Hamilton Depression Rating Scale (17-item) score	23.49 ± 5.29 (11 to 38)
Standardised Mini Mental State Examination (SMMSE) score	28.90 ± 1.71 (22 to 30)
Hopkins Verbal Learning Test (HVLT) Recall score	24.77 ± 6.31 (11 to 36)
Trail Making B completion time (seconds)	100.28 ± 49.18 (42 to 310)

Over half (N = 41; 58.6%) the individuals in the study had attempted suicide at least once during their lifetime, ranging from 0 to 3 attempts (Mean = 0.9 ± 1.0) (see Table 6.2). Gender and age were not associated with reported suicide attempts but chronicity was, χ^2 (1) = .23, p = .634 and z = 1.24, p = .217 respectively. All of the inpatients with reported suicide attempts had chronic depression (N = 41, 58.6%). A reported history of childhood sexual trauma (N = 22; 31.4%) was not associated with a reported suicide attempt, χ^2 (1) = 2.65, p = .104. Likewise, a family history of suicide in a first-degree relative (parents, siblings, children) (N = 6; 8.6%) was not associated with a reported suicide attempt, χ^2 (1) = 1.72, p = .189. This finding should be interpreted cautiously due to limited power. Almost half the inpatient sample (N = 34; 48.6%) had at least one first generation family member with depression (parents, siblings, children) ranging from 0 to 3 family members with depression (M = 1.65 SD = 0.8).

Table 6.3

Non-hierarchical lifetime DSM-IV co-morbid psychiatric disorders in the inpatient sample

Disorder category	DSM-IV diagnosis	N (%)
Anxiety Disorders	Presence of any Anxiety disorder	31 (44.29)
	Generalised Anxiety	16 (22.86)
	Panic	6 (8.57)
	Agoraphobia	2 (2.86)
	Social Phobia	10 (14.29)
	Obsessive Compulsive	2 (2.86)
	Post Traumatic Stress	14 (20.00)
Eating Disorders	Anorexia Nervosa	9 (12.86)
Substance-Related Disorders	Presence of any substance related disorders	14 (20.00)
	Alcohol Dependence	10 (14.29)
	Substance Dependence	5 (7.14)
Personality Disorders	Presence of any Personality Disorder	20 (28.57)
	Dependent Personality	7 (10.00)
	Borderline Personality	13 (18.57)
	Obsessive-compulsive Personality	2 (2.86)

Table 6.4

Chronic medical conditions in the inpatient sample

Chronic condition category	Type	N (%)
Lifetime chronic conditions (from a predefined list of six national priority conditions)	Asthma	10 (14.29)
	Cancer	3 (4.29)
	Stroke	1 (1.43)
	Heart or circulatory condition	19 (27.14)
	Rheumatism or arthritis or gout	4 (5.71)
	Diabetes or high sugar levels	3 (4.29)
Current chronic conditions (self-reported conditions over the past 6 months)	Hayfever	4 (5.71)
	Sinusitis or sinus allergy	1 (1.43)
	Emphysema	1 (1.43)
	Bronchitis	0 (0)
	Anaemia	0 (0)
	Epilepsy	3 (4.29)
	Fluid problems/Fluid retention/Oedema	4 (5.71)
	Hernias	0 (0)
	Kidney problems	0 (0)
	Migraines	5 (7.14)
	Psoriasis	0 (0)
	Stomach ulcer or other gastrointestinal ulcer	1 (1.43)
	Thyroid problems	10 (14.29)
	Tuberculosis	0 (0)
	Back or neck pain	11 (15.71)

6.4.3 Psychiatric and medical co-morbidity. Two thirds of the inpatient sample (N = 46; 65.7%) had at least one lifetime co-morbid DSM-IV psychiatric condition (*M* = 1.1; *SD* = 1.2; *mdn* = 1; range 0-5) (see Table 6.3). There were no significant gender difference in the mean number of lifetime co-morbid DSM-IV psychiatric conditions, z = 1.00, p = .317. Anxiety disorders were the most common lifetime DSM-IV co-morbid disorders followed by personality disorders and substance-related disorders (see Table 6.3). More specifically, DSM-IV Generalised Anxiety Disorder, Post-traumatic Stress Disorder and Borderline Personality Disorder were the most common lifetime DSM-IV co-morbid disorders in the inpatient sample. Females in the inpatient sample were more likely to have a Borderline Personality Disorder, χ^2 (1) = 5.95, p < .015. No gender differences were found for Generalized Anxiety Disorder and Post-traumatic Stress Disorder, χ^2 (1) = .05, p = .826 and χ^2 (1) = .29, p = .591 respectively.

Medical co-morbid conditions were coded to be comparative to the 2007 NSMWB and are presented in Table 6.4. On average the inpatient sample had between 0 and 5 (mean = 1.1; SD =

1.2; median = 1) co-morbid lifetime and current chronic medical conditions. In addition to the co-morbid conditions outlined in the 2007 NSMWB (see Table 6.4), inpatients in the sample also reported having the following medical conditions, hepatitis C (N = 2; 2.86%), sleep apnoea (N = 4; 5.7%), fibromyalgia (N = 3, 4.3%), chronic fatigue (N = 4; 5.7%), gastro-oesophageal reflux disorder (GORD) (N = 9; 12.9%) and chronic pain (N = 8; 11.4%). A higher number of chronic medical conditions (Table 6.4) was significantly correlated with current age, r (68) = .45, p <.001. There was no association of gender with the total number of chronic medical conditions, z = .33, p = .743.

6.4.4 Cognitive functioning. Three tests of cognitive functioning were performed during the interview/assessment. The Standardised Mini-Mental State Examination (SMME) was employed and the inpatient sample had on average normal cognitive functioning ranging from mild cognitive impairment to normal cognitive functioning (*M* = 28.9; *SD* = 1.71; range 22 to 30). Participants had an average Hopkins Verbal Learning Test (HVLT) recall score of 24.8 (*SD* = 5.3; range 11 to 36) indicating that majority of participants had normal cognitive functioning. However, a minority of participants (N = 5) had a HVLT recall score below 14.5, which has been reported as a conventional cut-off for dementia (Hogervorst, Combrinck, Lapuerta, Rue, Swales, & Budge, 2002; Brandt, 1991). The Trail Making B is a test of visual attention and task switching and is scored by recording the amount of time it takes to complete the test in seconds. The total sample had an average time of completion of 100.3 seconds ranging from 42 to 310 seconds (*mdn* = 88.5; *SD* = 49.2). The inpatient sample Trail Making B mean and median is higher than the normative mean for the test indicating cognitive impairment (50% percentile for age group 35 to 44 years old = 58 seconds) (Strauss, Sherman & Spreen, 2006). Impairments in visual attention and task switching are well-described features of severe depression (Ravnkilde et al., 2002). In fact, the Trail Making B mean found in the current study is on par with the mean reported in a previous study of depressed inpatients (N = 40; Trail Making B *M* = 101.0 seconds)

All three tests of cognitive functioning (SMMSE, HVLT and Trail Making B) were highly correlated with one another (Trail Making B and SMMSE, r(68) = -.46, p < .001; Trail Making B and HVLT, r(68) = -.56, p < .001; SMMSE and HVLT, r(68) = .51, p < .001). Current age at time of interview/assessment was moderately correlated with the Trail Making B test, r (68) = .24, p < .041. The other two tests were not correlated with current age at time of assessment (Age and HVLT, r (68) = -.11, p = .348; Age and SMMSE, r (68) = .10, p = .420). There were no gender differences on the three tests of cognitive functioning (SMMSE, z = -1.02, p = .309; HVLT, z = 1.32, p = .188; Trail Making B, z = .22, p = .827).

A lifetime history of ECT (N = 41; 58.6%) was associated with a lower HVLT recall score (*M* = 22.4; *SD* = 6.2), a lower SMMSE score (*M* = 29.6; *SD* = .56) and a longer time to complete

the Trial Making B test (*M* = 116.0; *SD* = 56.13) indicating poorer cognitive functioning in patients who had received ECT as treatment for their depression during their lifetime, z = 3.64, p < .001; z = 3.05, p < .002 and z = -3.05, p < .002 respectively. There were no differences between inpatients who had ECT during the index admission (N = 25) and inpatient who did not have ECT during the index admission (N = 45) on the SMMSE and Trail Making B test, z = .67, p = .500 and z = -.10, p = .917. However, inpatients who did receive ECT during the index admission had a significantly lower HVLT score, z = 2.57, p < .010. After controlling for age and treatment resistance using the composite TRD index, the relationship between recent ECT and HVLT score maintained its significance in an OLS regression, β = -3.78, t = -2.36, p < .021.

6.4.5 Hospitalisation. Participants were recruited and assessed while in hospital for treatment for their depression. This admission is referred to as the index admission. The average length of stay for the index admission was 60.1 days (*SD* = 64.93 days; range 5 to 361 days). Participants had a mean of 5.1 previous admissions (*SD* = 8.72; range 0 to 39) to same mental health facility prior to the index admission.

6.4.6 Treatment history. Table 6.5 lists the number and type of physical and psychological treatment trials undergone by the inpatients in the sample during their lifetime. Participants had received an average of 5.0 antidepressant trials ranging from 1 to 13 trials. During their lifetime, participants had received either a selective serotonin reuptake inhibitor (SSRI) (N = 58; 82.9%) and/or tricyclic antidepressant (N = 30; 42.9%) and/or serotonin-norepinephrine reuptake inhibitor (SNRI) (N = 61; 87.1%) and/or monoamine oxidase inhibitor (MAOI) (N = 12; 17.1%). A greater number of lifetime antidepressants trials was significantly correlated with a longer lifetime depression illness duration, *r* (68) = .37, p < .002. Medical chart auditing and patient recall found that the sample as a whole had trialled 353 antidepressants. From the trial duration data available (N = 251), 17.5% (N = 44) of all antidepressant trials had durations greater than one year (range 1 to 20 years). The remaining trials (N = 207; 82.5%) had trial durations less than one year. The mean doses of antidepressant trials are reported in Table 6.5.

In addition to antidepressant therapy, over 40% of the sample (N = 29; 41.4%) had received medication augmentation strategies (as defined by the ATHF) as treatment for their depression. The number of augmentation medication strategies ranged from 1 to 3 with the most common strategy being lithium (N = 24; 82.8%) followed by lamotrigine (N = 11; 37.9%), thyroid hormone treatment (N = 8; 27.6%) and carbamazepine (N = 2; 6.9%).

Over half (N = 41; 58.6%) the participants had received ECT as treatment for their depression during the course of their illness and 61% (N = 25) of these participants had received ECT treatment during the index admission in hospital. Other physical treatments received by the inpatient sample include ketamine infusions (N = 2; 2.9%), transcranial magnetic stimulation

(TMS) (N = 2, 2.9%), vagus nerve stimulation (VNS) (N = 1; 1.4%) and deep brain stimulation (DBS) (N = 1; 1.4%).

The entire sample had participated in inpatient psychotherapy programs and 90% of the sample had received individual psychotherapy sessions with a psychologist during the index admission. Approximately 59% of the sample had seen a psychologist outside of the index admission as an outpatient (see Table 6.5). All participants had received psychotherapy from their treating psychiatry as an outpatient or inpatient.

Table 6.5
Treatment history of the inpatient sample

Treatment history	N (%); Mean ± SD
Number of previous antidepressant trials	5.03 ± 2.97 (1 to 13)
Antidepressants trialled and mean dose (mg)	
Agomelatine	11 (15.71); 39.09 ± 18.28 (25 to 80)
Amitriptyline	12 (17.14); 37.22 ± 43.60 (10 to 125) [a]
Bupropion	6 (8.57); 102.00 ± 65.73 (30 to 150) [b]
Citalopram	13 (18.57); 22.5 ± 12.58 (10 to 40) [c]
Clomipramine	10 (14.29); 153.13 ± 87.05 (25 to 250) [d]
Desvenlafaxine	20 (28.57); 128.13 ± 89.38 (50 to 400) [e]
Dosulepin (dothiepin)	9 (12.86); 200 ± 90.83 (75 to 300) [a]
Doxepin	1 (1.43) [b]
Duloxetine	37 (52.86); 90 ± 41.69 (30 to 180)[f]
Escitalopram	30 (42.86); 32.5 ± 29.43 (10 to 150)[g]
Fluoxetine	29 (41.43); 49.47 ± 20.41 (20 to 80)[h]
Fluvoxamine	7 (10.00); 214 ± 116.10 (20 to 300)[d]
Imipramine	3 (4.29); 325 ± 176.78 (200 to 450)[b]
Mianserin	10 (14.29); 50.06 ± 43.67 (.50 to 140)[d]
Mirtazapine	36 (51.43); 51.43 ± 25.63 (15 to 90)[g]
Moclobemide	3 (4.29); 600 ± 519.62 (300 to 1200)
Nefazodone	1 (1.43); 300
Nortriptyline	9 (10.00); 100 ± 50 (25 to 150)
Paroxetine	15 (21.43); 20 ± 8.66 (10 to 40)[f]
Phenelzine	2 (2.86); 10[b]
Reboxetine	11 (15.71); 7.27 ± 1.62 (4 to 8)
Sertraline	27 (38.57); 148.82 ± 94.86 (10 to 300)[h]
Tranylcypromine	10 (14.29); 21 ± 12.87 (10 to 50)
Venlafaxine	41 (58.57); 266.96 ± 126.94 (75 to 600)[i]
Physical treatments trialled	
Antidepressants	70 (100)
Electroconvulsive therapy (ECT)	41 (58.57)
Augmentation	29 (41.43)
Ketamine infusions	2 (2.86)
Transcranial magnetic stimulation (TMS)	2 (2.86)
Vagus Nerve stimulation (VNS)	1 (1.43)
Deep Brain Stimulation (DBS)	1 (1.43)

[a] Missing dose data (N = 3); [b] Missing dose data (N = 1); [c] Missing dose data (N = 9); [d] Missing dose data (N = 2); [e] Missing dose data (N = 4); [f] Missing dose data (N = 6); [g] Missing dose data (N = 8); [h] Missing dose data (N = 10); [i] Missing dose data (N = 13)

6.4.7 Treatment resistance. The treatment history detailed above was used to rate the inpatients with TRD on the five staging models. Over 75% of the sample had failed greater than two antidepressants (N = 54; 77.1%) and had moderate to high levels of TRD as indicated by the medians on the available staging modes (Table 6.6). This finding should be considered in the

context of not being able to determine the adequacy of each treatment trial due to missing data on key variables such as dose, duration and response. The five staging models of TRD were significantly intercorrelated (see Figure 6.1). All pairwise correlations between the models remained significant at the $p < .001$ level after controlling for multiple comparisons with Bonferroni correlations (Figure 6.1). The high pairwise correlations between the models suggest a substantial degree of agreement between models on their ratings of TRD. In addition, the high pairwise correlations between the models imply that the five models of TRD are measuring the same underlying concept.

Table 6.6

Treatment resistance as scored by the existing TRD models

Models	N (%); Mean ± SD	Coefficient of variation (CV)
ATHF score	11.99± 7.82 (2 to 38); Median 9	65.3%
TRM score	2.44 ± 1.22 (0 to 5); Median 2	50.0%
ESM score	2.94 ± 2.34 (0 to 7); Median 2	79.6%
MGHS score	6.61 ± 4.23 (0 to 18); Median 6.75	64.0%
MSM score	9.51 ± 2.32 (3 to 14); Median 9	24.4%

ATFH, Antidepressant Treatment History Form; TRM, Thase and Rush Model; ESM, European Staging Model; MGHS, Massachusetts General Hospital Staging Model; MSM, Maudsley Staging Method

The interrelatedness between the models provided the opportunity to create a TRD index, which combined the five TRD models into the one index and allowed for the underlying construct of TRD to be measured rather than one specific interpretation of TRD. Scores on all five models of TRD were standardised into z-scores and then summed to create the TRD index. The mean of the TRD index is 0 (SD = 4.5; range -8.2 to 11.2). Scores above 0 indicate TRD scores above the mean and scores below 0 indicate scores below the mean. The benefit of creating a TRD index is that it allows for greater variability in the inpatient sample across the models.

In order to test whether the TRD index improves the variability of TRD scores a coefficient of variation (CV) was calculated for each model (see Table 6.6). The CV is a measure of relative variability and is expressed as a percentage with higher percentage indicating greater variability. It was not possible to calculate a CV for the TRD index as the TRD index had a mean score of 0. However, it was possible to visually inspect the distribution of the TRD index against the five existing models using a downloadable Stata add-on program called STRIPPPLOT (Cox, 2003)

(Figure 6.2). Using the CV, the ESM (CV = 79.6%) appears to have the greatest variability, however when visually inspecting the distribution (see Figure 6.2) the ESM's CV is likely to be influenced by a non-normal distribution and outliers. Additionally, the ATHF may also be influenced by numerous outliers despite having the highest variability as indicated by the largest inter-quartile range (see Figure 6.2). In contrast, when visually inspecting the TRD index the distribution appears to be flatter and have a more even distribution (see Figure 6.2). Thus the TRD index balances the strengths and weaknesses of the various existing TRD models and is less susceptible to outliers whilst retaining sound variability (see Figure 6.2). The five models of TRD and the TRD index are plotted on their own ordinal scale with their maximum score, minimum score, interquartile range and median displayed as a box-and-whisker plot. Above each box-and-whisker plot the distribution of scores for each model and the TRD index are shown (see Figure 6.2).

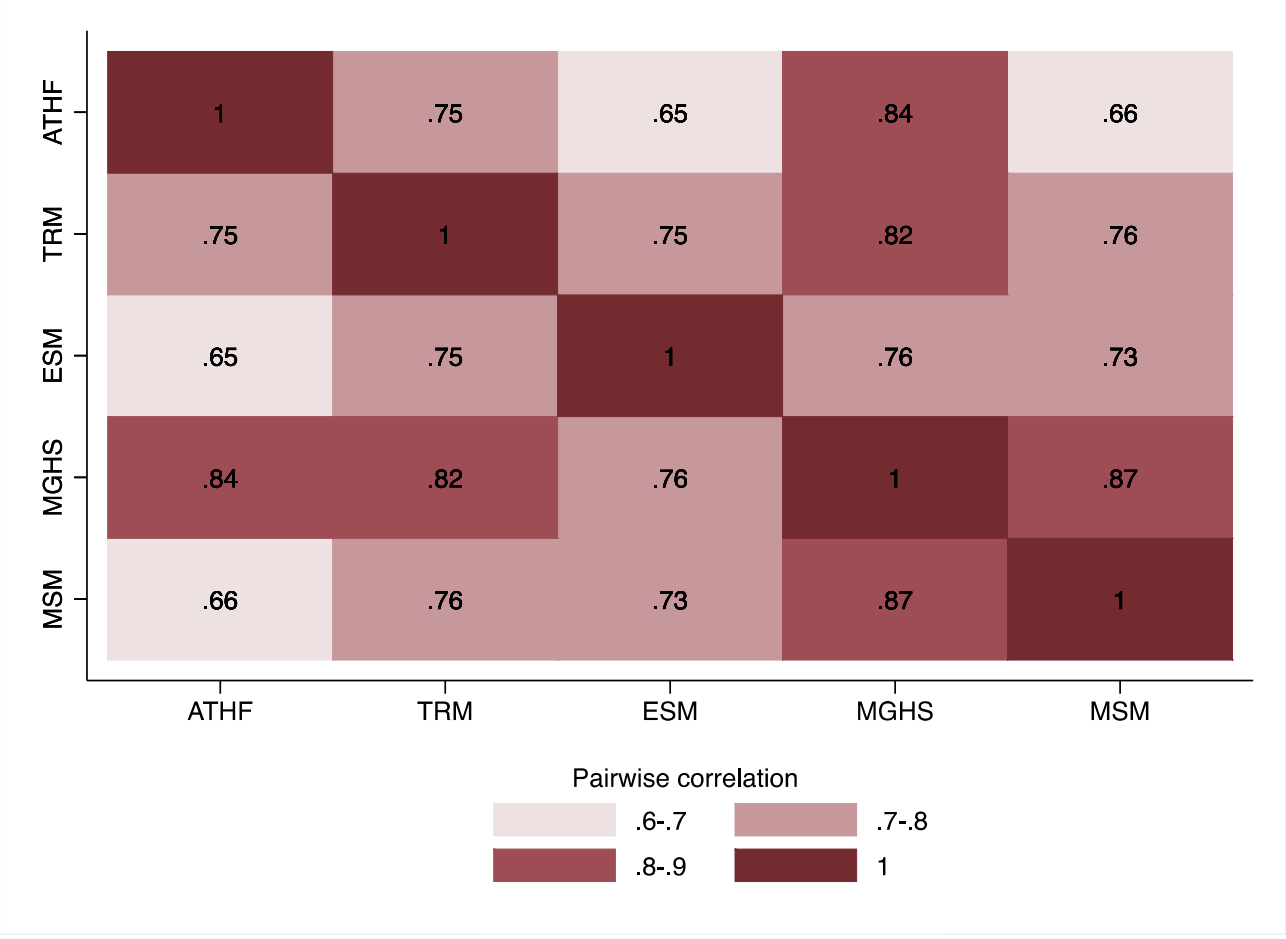
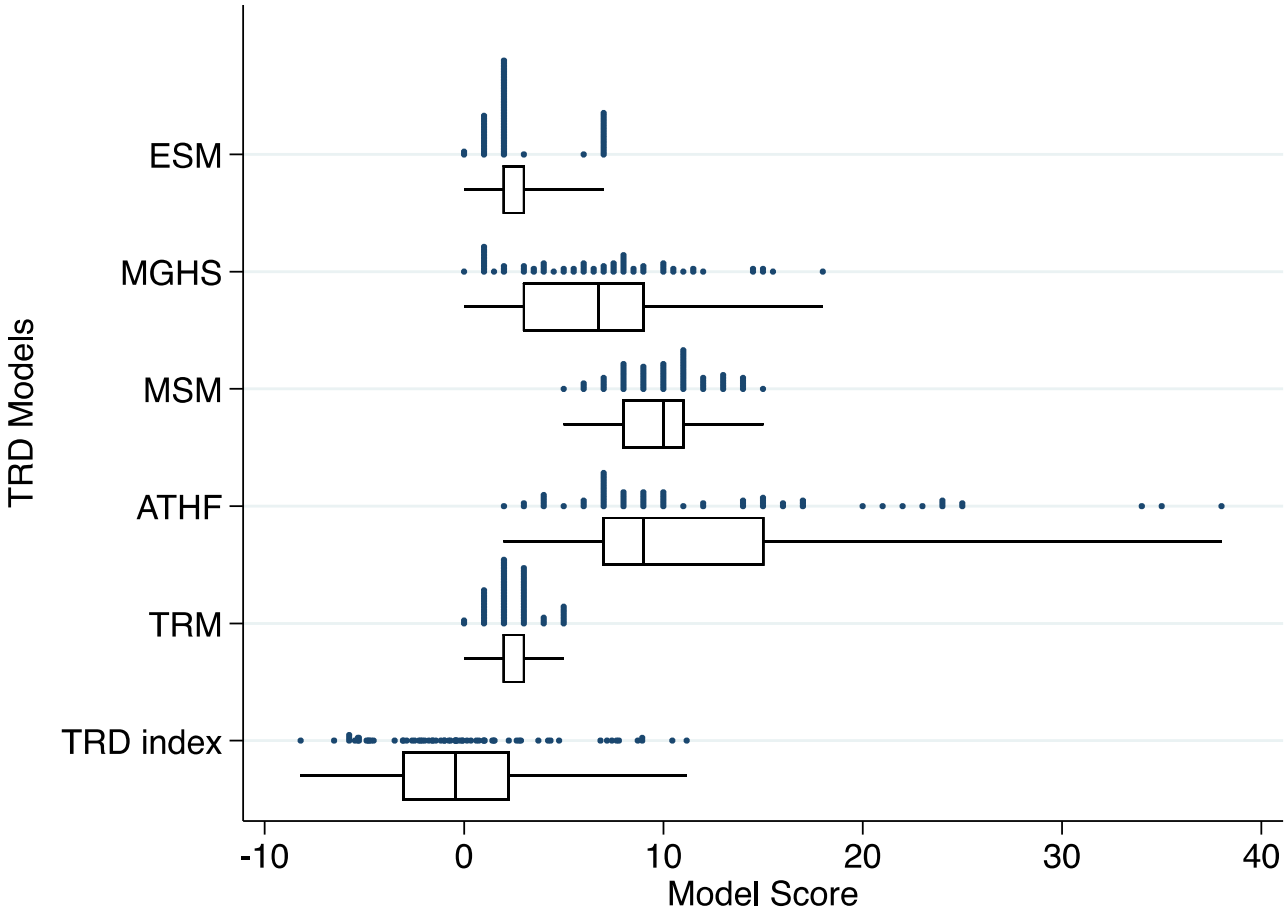


Figure 6.1. Plot matrix displaying the pairwise correlations between the five available staging models for TRD



Note. For each model and TRD index the maximum score, minimum score, interquartile range and median are displayed as a box-and-whisker plot. Above each box-and-whisker plot, the distribution of scores is depicted as a frequency histogram for each model and TRD index.

Figure 6.2. The five existing TRD models and the composite TRD index are plotted on their own ordinal scales in order to compare the variability and distributions.

6.4.8 Exploring predictors of TRD. The predictors of TRD were explored with two regression models (see Table 6.7). The first model was an OLS regression with the newly created TRD index as the outcome variable. The second model was logistic regression model with the definition of the failure of three or more antidepressants as the outcome variable. The purpose of performing two models was to compare a continuum rating of TRD to a dichotomous definition of TRD to test whether they conceptualise TRD similarly and whether conceptualising TRD dichotomously is a valid approach. The most commonly reported definition of TRD in medical

scientific literature is the failure of two antidepressants. There was very little power to test the definition of the failure of two antidepressants as the majority of the inpatient sample (N = 64; 91.4%) had failed two or more antidepressants. Therefore the dichotomous definition tested in Model 2 is the failure of three of more antidepressants (N = 54; 77.1%).

The two models were compared for predictive utility and goodness-of-fit. The same predictor variables were added to each model to determine whether there are any differences in the predictive utility of the variables across the models. As the MSM model incorporates symptom severity, number of antidepressant treatments, duration of illness and treatment strategies (i.e. ECT and augmentation) these variables will not be included in the regression models due to potential multicollinearity. Variables were entered into the regression models based on predictors identified in previous literature including poorer occupational functioning and disability, co-morbidity, early adverse events, and a history of suicide attempts. Both regression models were controlled by gender and age. To explore the predictors of TRD, several other clinical variables were entered into the regression models: psychological distress, cognitive functioning, number of chronic medical conditions, age of onset and family history. The HVLT score was added as the measure of cognitive functioning in the models rather than the SMMSE or the Trail Making B Test because it had superior independent predictive utility in an OLS regression model predicting TRD index. There was no evidence of multicollinerarity between the predictors with tolerance values greater than 0.1 and a mean variance inflation factor (VIF) of 1.4. In order to compare the regression models, the same eleven variables were added to each model (see Table 6.7).

Table 6.7
Predicting TRD using OLS regression (Model 1) and multivariate logistic regression (Model 2)

	Model 1: TRD Composite Index					Model 2: Failure of three or more antidepressants				
Predictors	Beta	Standard error	t	95% CI	p	OR	Standard error	Z	95% CI	p
Age (years)	.14	.05	2.92	.04 - .24	.005	1.09	.05	1.83	.99 –1.19	.067
Gender										
Female	*Reference category*									
Male	-2.15	1.10	-1.96	-4.34 - .04	.054	.13	.12	-2.12	.02 -.86	.034
Income Source										
Disability pension	*Reference category*									
Other source of income i.e. employment	-1.44	1.05	-1.38	-3.54 - .66	.174	.25	.24	-1.45	.04-1.63	.147
Reported childhood trauma	-2.00	1.00	-1.99	-4.01 - .01	.051	.57	.52	-.62	.09-3.46	.538
Age of onset (years)	-.12	.05	-2.58	-.22 - -.03	.012	.97	.05	-.74	.88-1.06	.461
Number of suicide attempts	1.71	.47	3.62	.77 – 2.66	<.001	2.48	1.31	1.73	.89-6.98	.084
Number of 1st generation family members with depression	-.46	.50	-.91	-1.46 - .55	.366	.73	.35	-.66	.29-1.86	.509
Number of lifetime DSM-IV Axis I co-morbid psychiatric disorders	.53	.39	1.36	-.25 – 1.32	.180	2.95	1.70	1.88	.95-9.14	.061
Number of co-morbid medical conditions	.36	.43	.85	-.49 – 1.22	.397	1.55	.83	.82	.54-4.44	.411
K-10 score	-.16	.09	-1.78	-.35 - .02	.081	.98	.08	-.27	.83-1.15	.790
HVLT score	-.16	.08	-2.13	-.32 - -.01	.038	1.03	.07	.47	.90-1.19	.635

6.4.9 Comparing the regression models. The two regression models are displayed in Table 6.7 An interaction between current age and age of onset was tested but was not added into the final regression models due to non-significance. Model 1, an OLS regression model using the TRD composite index as the outcome variable was significant and explained 46% of the variance in the TRD index, F (11, 58) = 4.56, p < .001, R^2 = .46. Model 1 found four significant associations between the TRD index and the predictor variables. More specifically, the following variables significantly predicted higher TRD index scores: higher prevalence of suicide attempts, an older current age, an earlier age of onset, and poorer cognitive functioning on the HVLT. For Model 1, a White test (χ^2 (69) = .70, p = .444) found no presence of heteroscedasticity indicating that the variance of errors are constant.

Model 2, a logistic regression model using the dichotomous variable of the failure of three or more antidepressant trials (Yes, N = 54; No, N = 16) had a satisfactory goodness-of-fit when tested with the Hosmer–Lemeshow statistic (χ^2 = 3.00, p = .934). The only significant predictor in Model 2 was gender. Males were less likely to have failed three or more antidepressants compared to females. For Model 2, the area under the receiver operating characteristic (ROC) curve was .89 (95% CI .81 - .97) and the model correctly classified 85.7% of the inpatients who had failed three or more antidepressants with a sensitivity of 96.3% and a specificity of 50%.

When comparing the R^2 and pseudo R^2 of both models, Model 1 (R^2 = .46) explained more variance in the outcome variable than Model 2 (Pseudo R^2 = .39). Nominally when comparing the R^2 and pseudo R^2 , Model 1 appears to be superior. However, this cannot be substantiated due to the different statistical models used. Model 1 did provide greater understanding of what factors are associated with TRD when compared to Model 2. It is possible that the failure of three or more antidepressants is not an appropriate definition or criterion of TRD for this type of inpatient sample as the majority of participants had failed more than two antidepressants (N = 54; 77.1%), had a chronic illness duration (N = 64; 91.4%) and collectively had moderate levels of TRD as rated on each of the models of TRD.

6.5 Discussion

Over 90% of the inpatient sample had TRD according to the most common definition of TRD as the failure of two antidepressants and over 75% of the sample had failed three or more antidepressants. When TRD is rated on a continuum using staging models, the inpatient sample had on average a moderate to high level of TRD. On average the inpatient sample were chronically depressed, had trialled multiple treatment modalities including psychotherapy and ECT and were highly distressed at time of assessment. In addition the inpatient sample had poor occupational

functioning as evidenced by a significant minority of the sample on government disability pensions and over half the sample experiencing unemployment at time of assessment. There was also a high prevalence of suicide attempts amongst the sample with over half the sample attempting suicide at least once during their lifetime. This is line with the findings from the 2007 NSMHB (Chapter Four) which reported that individuals with chronic depression in the Australian community who are treated in tertiary care settings have a more complex presentation as indicated by more severe symptoms, greater psychiatric co-morbidity, a greater traumatic load, higher levels of disability and higher levels of current psychological distress. As previously noted (Chapter Four pp 107) chronically depressed individuals treated in tertiary care are more likely to attempt suicide compared to chronically depressed individuals treated in primary care and untreated individuals. This previous finding, in addition to, the high prevalence of suicide found in the inpatient sample elucidates to the high level of TRD and the highly complex presentations found in tertiary treatment settings.

By rating the depressed inpatient sample on all five staging models of TRD it allowed for a direct comparison between the models to determine whether the models rate TRD in a similar way. The five models of TRD have not been compared together in the one study previously. Consistent with the findings from a previous validation study which compared just two staging models (Petersen, et al., 2005), and which found the TRM and MGHS models to be highly correlated, the current study found that all five models were highly correlated with one another. All five models were shown to have good concurrent validity, as indicated by high correlations between the models. Despite the methodological differences between the models and the improvement and evolution of the models over time, they all generated similar ratings of TRD (see Figure 6.1). Due to this, an index of TRD was created to capture the agreement and similarity between the models.

A unique feature of the methodology of this thesis is the ability to rate treatment resistance on the five models of TRD. The index was used as an overall measure of TRD on a continuum and was compared to the dichotomous definition of TRD as the failure of three or more antidepressants. The purpose of comparing TRD rated on a continuum to the dichotomous definition of TRD was to assess which method of rating TRD provides more predictive utility. One of the main criticisms of defining TRD dichotomously is that it is too broad to conceptualise TRD appropriately. This criticism was supported by the current findings, as the model using TRD rated on a continuum had greater predictive utility and explained more of the variability in TRD. Only one factor was found to predict the failure of three or more antidepressants whereas the model predicting TRD using the TRD index found four predictors.

Earlier age of onset, a greater number of lifetime suicide attempts, poorer cognitive functioning on the HVLT and an older current age were significantly associated with TRD

composite index score. The significant associations between TRD score and an earlier age of onset and an older current age could indicate that individuals with higher levels of TRD have had a longer time to manifest a chronic illness and to have trialled many treatments with very little success. However, findings from the STAR*D, a large-scale clinical trial (N = 2876) of treatments for depression has shown that approximately one third of patients (33% cumulative non-remission rate) can trial and not respond to four antidepressants taken sequentially within a 12-month period (Howland, 2008; Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Findings from the STAR*D show that a chronic illness duration is not necessarily a requirement of TRD as it possible for patients to fail multiple treatment trials within a 12-month period. This conclusion was confirmed in the present study by a non-significant interaction, excluded from the final model, between current age and age of onset in the OLS regression model. Thus, earlier age of depression onset is likely a risk factor for higher levels of TRD, whereas, older current age may have a bidirectional relationship with TRD. This finding was replicated in the 2007 NSMHWB in community-residing Australians with chronic depression (see Chapter Four pp 110). Thus, chronic depression and TRD may be associated with older age as a temporal artefact or due to other factors also linked to older age such as cerebrovascular changes (see Chapter Four pp 110).

The finding that individuals with higher levels of TRD have a higher prevalence of suicide attempts may be a consequence of a chronic and a long-term refractory illness. Personality factors including hopelessness, neuroticism and extroversion have been associated with suicide attempts in persons with MDD (Brezo, Paris, & Turecki, 2006). Hopelessness and suicidal ideation have previously been linked to TRD (Papakostas, et al., 2003b). High levels of hopelessness and perhaps diminishing expectations that future treatments will result in remission may lead to suicidal ideation and eventual attempts at suicide in individuals with TRD. A population-based longitudinal survey of mental illness, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), found that a co-morbid borderline personality disorder was associated with suicide attempts in persons with MDD (Bolton, Pagura, Enns, Grant, & Sareen, 2010). However, it is not clear what effect personality disorders might have had on the prevalence of suicide attempts in our TRD sample, nor the extent to which the finding might have been biased by the inpatient status of our study participants. It is clear that individuals with higher levels of TRD are at a greater risk of suicide. Findings from the STAR*D identified that previous suicide attempts were more likely in outpatients receiving specialty care rather than primary care (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Previous suicide attempts together with chroncitiy may result in higher levels of specialty care treatment seeking and could explain the high prevalence of both phenomena in the current sample.

The current study found that poorer cognitive function, specifically poorer new learning ability, was associated with higher levels of TRD. It should also be noted that a minority of participants (N = 5) had a HVLT recall score below 14.5, which is the cut-off for dementia (Hogervorst, Combrinck, Lapuerta, Rue, Swales, & Budge, 2002; Brandt, 1991). It is possible that these individuals have pseudodementia, which is cognitive impairment due to their current depressed state, that resolves in response to treatment (Brown, 2005). Cognitive impairment in individuals with TRD could be a consequence of chronicity or treatment resistance. Alternatively, cognitive impairment in TRD may also be associated with recent ECT treatment. Recent ECT treatment was associated with poorer cognitive functioning (as measured by the HVLT) when controlling for age and TRD index. Therefore it is likely that ECT treatment is involved in poorer cognitive functioning in TRD. Alternatively, cognitive impairment may be a facet of depression. A recent review of cognitive functioning in MDD recognised that cognitive impairment may not resolve or improve despite symptom reduction and that subsequent episodes of depression may result in further decline of cognitive functioning (Hammar & Ardal, 2009). The majority of participants (91.4%) in the current study had a chronic illness duration over 2 years. Thus poorer cognitive functioning could be considered a consequence of chronicity rather than long-term effect of treatment. Poorer cognitive functioning together with the finding that chronic and TRD is associated with older age (see Chapter Four pp 110) may provide more support for cerebrovascular changes in chronic and TRD (Rao, 2000; Sheline, et al., 2010).

Further validation studies are required in depressed outpatients to generalise from these findings in inpatients and to further assess the clinical utility of using staging models of TRD in research and clinical practice. The use of chronic and severely treatment resistant inpatients might have reduced the generalisability of the findings. Further validation of the models should be repeated using depressed outpatients. Another limitation of the study was the lack of variability in the chronicity and symptom severity of the individuals in the sample. There were relatively few individuals in the study with mild or no treatment resistance. The reliability of the models, both inter-rater reliability and test-rest reliability, needs to be considered in future studies.

Presently these five models are our “gold standard” instruments to measure TRD in clinical and research populations. No one model was clearly superior at measuring TRD in this study. The phenomenon of TRD may not fully be understood until genetic and neurobiological endophenotypes are identified and incorporated into models. Consistency in research methodology, leading to replicable findings is needed so that we can start to identify individuals who may be resistant to treatment earlier and reduce the long-term disease burden posed by TRD.

Chapter Seven

The underlying personality structure of depressed inpatients and the association between personality and treatment-resistant depression (TRD)

7.1 Introduction

This chapter examines the underlying personality structure of depressed inpatients and the association between personality and treatment resistance. The identification of distinct personality profiles in depression has the potential to provide insight into the development, course and maintenance of the disorder. There is a well-established relationship between depression and personality and there is evidence to suggest that personality may play a role in treatment response. The majority of studies assessing personality and depression have been conducted in non-clinical and outpatient samples with very few studies assessing personality in inpatient samples. Additionally, there have been few studies that have assessed personality in TRD and investigated whether personality structures are associated with TRD using the five available models TRD. Assessing the personality structure in depressed inpatients and determining whether there is an association between treatment resistance and personality structures could be useful in treatment planning, identifying patients at risk of poor treatment response and identifying those on a chronic illness trajectory. The analysis for this chapter was developed to address the following research question:

RQ6: What is the underlying personality structure of depressed inpatients and is there an association between personality and TRD?

To address this research question, the personality structure of depressed inpatients was assessed using the five-factor model (FFM) of personality. Firstly, inpatients' self-reported ratings of personality are compared to informant ratings of inpatients' premorbid personality to determine whether inpatients ratings of personality are likely to be valid and not dependent on their current depressed state. Likewise, the association between current psychological distress and symptom severity on personality was assessed to determine whether personality is influenced by the inpatients' current depressed state.

The five-factor model of personality was developed in non-clinical samples as an assessment of normal personality. Therefore it was imperative to assess the differences between the inpatient sample and healthy controls to determine how the inpatient sample varied on particular personality factors. The inpatient sample was also compared to a more treatment responsive

depressed sample to assess how personality differs between currently depressed inpatients and previously depressed outpatients with supposedly better treatment outcomes.

In order to assess the association between personality and TRD, the five personality domains were included as predictors of TRD alongside sociodemographic and clinical variables (see Chapter Six pp 155) using an index of TRD as the outcome variable in a regression model.

7.2 Background

Throughout history the relationship between personality and depression has been studied extensively. The Ancient Greek philosopher Aristotle (384 – 322 BC) was one of the first to hypothesise a relationship between personality and depression. He theorised that certain individuals are naturally of a melancholic character and may be vulnerable to developing a depressive disorder (Lawlor, 2012). Prior to Aristotle, Hippocrates (460 – 370 BC) implicated "humors" as the cause of particular personality traits and psychopathology (Klein, Kotov & Bufferd, 2011). The interest in the association between personality and depression has continued into modern times and has important implications in research and clinical practice.

The identification of distinct personality profiles in people with depression has the potential to provide insight into the development, course and maintenance of the disorder over time (Klein, Kotov & Bufferd, 2011). Furthermore, personality may be useful in identifying subgroups of depression which differ in aetiology and illness course and may help to create more clinically and aetiological relevant classification systems (Brown & Barlow, 2009; Klein, Kotov & Bufferd, 2011). In the clinical setting, personality may be useful in identifying persons at risk of developing depression, tailoring treatment, explaining psychiatric co-morbidity and predicting treatment response (Klein, Kotov & Bufferd, 2011; Quilty et al., 2008). A future direction in depression research may involve the use of phenotypic personality traits as targets for genetic and neurobiological research which could provide more understanding of the disorder above and beyond what is provided by current depressive diagnoses (Canli, 2008; Klein, Kotov & Bufferd, 2011).

The consideration of personality in research and clinical practice may further our understanding of treatment resistant and chronic forms of depression and may help to select and optimise treatment for these populations. Likewise the study of personality may provide crucial information needed to advance current diagnostic classification systems (Bagby et al., 2008) and conceptualise the phenomenon of treatment-resistant depression more appropriately.

7.2.1 Models of Personality and Depression. The relationship between personality and depression has been explained in several ways (Akiskal, Hirschfeld, & Yerevanian, 1983, Malouff, Thorsteinsson, & Schutte, 2005; Klein, Kotov, & Bufferd, 2011). Eight putative associations

between personality and depression have been proposed: 1) depression and personality overlap conceptually and have common causes; 2) personality and depression form a continuous spectrum; 3) personality is a precusor to depression; 4) personality contributes to the manifestation of depression; 5) personality has a pathoplastic effect on depression; 6) personality is state dependent, related to current depressive symptoms; 7) depression alters personality over time; and 8) depression and personality are not directly related, a third variable mediates the relationship (Akiskal, Hirschfeld, & Yerevanian, 1983, Malouff, Thorsteinsson, & Schutte, 2005, Klein, Kotov, & Bufferd, 2011). Table 7.1 summarises the proposed associations between personality and depression.

Table 7.1

Associations between personality and depression

Model	Proposed association between personality and depression
1. Common cause	Shared aetiology account for the observed association
2. Spectrum	Similar aetiology; association is fairly specific and nonlinear
3. Precusor	Similar aetiology; personality predicts onset
4. Predisposition	Personality predicts depression onset other variables may moderate this link
5. Pathoplasticity	Personality predicts variation in presentation and outcomes of depression
6. State-effect	Personality is altered during a depressive episode but returns to premorbid level after episode resolves
7. Scar-effect	Personality is altered during and after a depressive episode
8. Mediation	Personality and depression are not related other variables mediate the relationship

Adapted from Klein, Kotov, & Bufferd, 2011

As reviewed by Klein, Kotov and Bufferd (2011), the eight associations of personality and depression can be summarised into three main theories. The first theory, endorsed by the common cause, spectrum, precursor and mediation models, suggests personality and depression have similar aetiologies but depression and personality are not directly related, a third variable mediates the relationship (Klein, Kotov, & Bufferd, 2011). The predisposition and pathoplasticity models endorse the second theory that personality contributes to the onset, maintenance and course of depression over time (Klein, Kotov, & Bufferd, 2011). The final theory (state and scar effect models) suggests that depression may alter personality by distorting personality during a depressive

episode (Klein, Kotov, & Bufferd, 2011). At the resolution of a depression episode personality is thought to either return to the pre-morbid profile (state-effect) or personality alterations persist post recovery (scar-effect) (Klein, Kotov, & Bufferd, 2011).

Theories of personality and depression have garnered considerable attention in the medical scientific literature. However, they have been difficult to validate or test consistently due to the difficulties surrounding personality assessment. The main pitfalls surrounding personality assessments, particularly in clinical populations, are how to define maladaptive or pathological personality, the stability of personality over the lifespan, the validity of personality disorder diagnoses and the accuracy of self-reported ratings of personality. Despite the outlined conceptual and methodological issues, understanding the role of personality plays in the aetiology of depression, response to treatment and help seeking behaviours, is crucial for both research and clinical practice.

7.2.2 Personality dimensions and depression. How personality is conceptualised and assessed in both research and clinical practice is imperative when considering the interplay between personality and depression. The predominant taxonomy of personality structure is the "Big Five" model which measures five trait dimensions of personality: Neuroticism (N; easily upset, maladjusted, not calm); Extraversion (E; assertive, energetic, talkative); Openness (O; imaginative, independent-minded, intellectual); Agreeableness (A; cooperative, good-natured, trusting); and Conscientiousness (C; dependable, orderly, responsible) (Costa & McCrae, 1991; Malouff, Thorsteinsson, & Schutte, 2005). The five factor model was developed using the lexical hypothesis by sampling the English language and determining from thousands of adjectives the most salient and socially relevant behavioural dispositions in individuals (Grice, 2005). The greatest criticism of this approach is that the five factor model is atheoretical and is perhaps too narrow to conceptualise the complex nature of human personality (Costa & McCrae, 1995; Grice, 2005). Nonetheless, the five factor model of personality is the most widely accepted and used measure of personality utilised by social, clinical and organisational fields of study (Costa & McCrae, 1995).

Although initially developed in non-clinical populations there is now sufficient evidence to suggest that the five-factor model is suitable for use in clinical populations (Costa Jr & McCrae, 2010, Costa & McCrae, 2009, O'Connor, 2005). Evidence suggests that the five-factor model can measure personality abnormalities as extreme variants of the five dimensions (neuroticism, extraversion, openness, agreeableness and conscientiousness) and these maladaptive variants can be consistently related to psychopathology (Costa Jr & McCrae, 2010, Costa & McCrae, 2009, O'Connor & Dyce, 2001, O'Connor, 2005; Widiger & Costa, 2002).

An early meta-analysis (N = 33 studies) identified a personality profile of high neuroticism, low conscientiousness, low agreeableness and low extraversion across various psychiatric disorders

including depression (Malouff, Thorsteinsson, & Schutte, 2005; Trull, 2012). More specifically, depression has repeatedly been associated with high levels of neuroticism and low extraversion (Akiskal, Hirschfeld, & Yerevanian, 1983; Harkness et al., 2002, Fanous, Neale, Aggen, & Kendler, 2007; Katon, et al., 2002; Kotov, Gamez, Schmidt, & Watson, 2010; Mulder, 2002; Rosellini & Brown, 2011). There is evidence to suggest that high neuroticism is a risk factor for depression (Barnhofer and Chittka, 2010; Griffith et al., 2010) predicts the onset of depression (Fanous, Neale, Aggen, & Kendler, 2007) and is associated with worse treatment outcomes (Mulder, 2002) and a reduced likelihood of remission in depression (Katon, et al., 2002).

Of the five personality dimensions, neuroticism is the most consistently reported dimension associated with depression and refers to the tendency to respond to threat, frustration and loss with negative emotions (Costa & McCrae, 1992; Lahey, 2009). A chronic negative affect, difficulty inhibiting impulses, unrealistic expectations, unfounded somatic complaints and dependence on others are dysfunctional behaviour patterns exhibited by individuals with high levels of neuroticism (Widiger, Costa Jr, & McCrae, 2002).

Not as widely studied in relation to depression are the personality dimensions of openness, agreeableness and conscientiousness (Rosellini & Brown, 2011). There is limited evidence to suggest a link between depression and low conscientiousness (Anderson & Mclean, 1997; Trull & Sher, 1994). One study found that in sixty-three depressed inpatients, the personality dimension of conscientiousness was one standard deviation below the norm at discharge (Costa & McCrae, 1985) and at a 6-month follow-up post discharge (Anderson & McLean, 1977). The authors theorised that low conscientiousness in depression could be related to varied task performance and repeated performance failures leading to increased stress and symptoms of depression (Anderson & McLean, 1997). Furthermore, an additional study found high openness and low conscientiousness alongside high neuroticism and low extraversion predicted a lifetime diagnosis of MDD (Trull & Sher, 1994). The five-factor model of personality provides a broad overview of personality and has proven its usefulness in identifying the personality profiles associated with the risk, onset and course of depression.

7.2.3 Cognitive styles and depression. The forefather of the cognitive therapy, Aaron Beck defined personality as a "relatively stable organisation of cognitive, behavioural, motivational and physiological schemas for representing adaptive or maladaptive responses to the normal demands and stresses of everyday life" (Clark & Beck, 1999 cited in Zukerman, 2011). In line with his cognitive theory of psychological disorders and cognitive theory of depression, Beck postulated the existence of maladaptive schemas which reflect deep-seated patterns of distorted thinking about oneself, relationships with others and the world (Zukerman, 2011). The three primary depressive schemas are negative views of self, experiences and the future (Zukerman, 2011). These depressive

schemas are thought to correspond to low self-esteem (views of self), cognitive distortions (views of experiences) and attitude of hopelessness (views of the future) which are consistently reported in depressed patients (Zukerman, 2011). According to Beck, negative schemata are vulnerability factors for the development of depression as they predispose towards a negative interpretation of life events and views of self (Beck, 1967, Wegener et al., 2013).

There is evidence to suggest that negative cognitive styles and dysfunctional attitudes are predisposing factors to depression and may predict a poorer illness course in individuals with depression (Iacoviello et al., 2006). Using data from the Temple-Wisconsin Cognitive Vulnerability to Depression Project, one study followed non-depressed participants (N = 159) at baseline who developed episodes of depression throughout the course of the study for a 2.5 year period (Iacoviello et al., 2006). At baseline, participants completed the Cognitive Style Questionnaire (CSQ) and the Dysfunctional Attitudes Scale (DAS) to determine the type of cognitive style. Participants with a negative cognitive style at baseline, before experiencing depression episodes, experienced a greater number of episodes, more severe episodes and a more chronic illness compared to participants with and a more chronic illness compared to participants with a positive cognitive style at baseline (Iacoviello et al., 2006).

7.2.4 Personality traits and treatment response in depression. The relationship between personality and depression extends beyond the risk, onset and maintenance of the disorder and has been implicated in treatment response (Gorwood et al., 2010, Hayward et al., 2013, Katon et al., 2002, Mulder, 2002). In the broadest sense, personality dysfunction as measured by the Standardised Assessment of Personality – Abbreviated Scale (SAPAS) has predicted poorer short-term (6 weeks) response to antidepressant treatment in a large sample of depressed outpatients (N = 8229) (Gorwood et al., 2010). Reviewing the five factor model and treatment response, a large systematic review (N = 50 studies) identified high neuroticism as a predictor of worse treatment outcomes particularly over a long-term follow-up period (Mulder, 2002). The review conducted by Mulder (2002), highlighted the need for future studies to control for clinical characteristics that also impact treatment response such as, symptom severity and chronicity, in order to gain an accurate reflection of the role personality plays in treatment response.

An early study assessed the five factor model of personality in depressed outpatients (N= 57) prior to treatment entry and three months after commencing treatment (Bagby et al., 1995). All depressed outpatients in the study received antidepressant treatment and were assessed at a 3-month follow-up to determine response (defined as a 50% reduction in 17- item HAM-D score) (Bagby et al., 1995). Neuroticism was associated with depressed mood at treatment entry and a decrease in neuroticism at the follow-up was associated with a response to treatment (Bagby et al., 1995). The depressed outpatients who responded to treatment (N = 41) maintained a score of neuroticism one

standard deviation above the normative mean suggesting neuroticism may be a predisposing factor to depression (Bagby et al., 1995). Response to treatment was also associated with an increase in extraversion scores (Bagby et al., 1995). The domains of openness, agreeableness and conscientiousness were not found to be altered by depression severity or treatment response (Bagby et al., 1995). The authors concluded that neuroticism may be a vulnerability factor to depression and extraversion is the strongest personality predictor of treatment response (Bagby et al., 1995).

While there have been various studies investigating personality and treatment response in depression there have been very few studies assessing personality in depressed samples employing a standardised definition of TRD. A brief report by Kaplan and Klinetob (2000) found higher scores on the Minnesota Multiphasic Personality Inventory (MMP1-2) subscales (all except hypomania) in outpatients with TRD compared to individuals with non-TRD (Kaplan & Klinetob, 2000). In the report, the Thase and Rush (1997) model of TRD was used to classify outpatients with TRD (N = 20) and non-TRD (N = 20) (Kaplan & Klinetob, 2000). The TRD and non-TRD patients were similar on the reported demographic variables including age, gender ratio and marital status (Kaplan & Klinetob, 2000). Unsurprisingly, the TRD outpatients had trialled more antidepressants and had more psychotherapy interventions than the non-TRD patients (Kaplan & Klinetob, 2000). In addition the TRD outpatients had poorer occupational functioning (40% were receiving disability pensions for their depression), were more likely to have co-morbid anxiety diagnosis and reported higher levels of trauma and emotional abuse than the non-TRD patients (Kaplan & Klinetob, 2000).

The authors theorised that TRD may be related to childhood traumatic experiences with early adverse experiences resulting in an increased vulnerability to life stressors (Kaplan & Klinetob, 2000). When reviewing the precipitants to their depressed episode, the TRD outpatients in Kaplan and Klinetob's (2000) report perceived their precipitants as "traumatic". However when reviewed by the authors, the reported "traumatic" experiences were more likely to be perceived in the normal population as stressful life events such as, job stress and divorce (Kaplan & Klinetob, 2000). Thus, high scores on all MMPI-2 domains (except hypomania) may indicate maladaptive psychological defences to deal with "normal" life stressors (Kaplan & Klinetob, 2000).

A more recent study assessed the personality profile of patients with TRD (N = 35) compared to patients with remitted depression (N = 27) and healthy controls (N = 66) using the five factor model (Takahashi et al., 2013). The definition of TRD employed was the non-response to at least two antidepressants (Takahashi et al., 2013). The TRD sample had significantly higher neuroticism and lower extraversion, openness and conscientiousness scores on the NEO-PI compared to healthy controls and patients with remitted depression (Takahashi et al., 2013). The authors propose that low openness may be a feature unique to TRD and maybe be related to lower levels of resilience (Takahashi et al., 2013). This is line with the conclusions presented by Kaplan

and Klinetob (2000) who propose that TRD outpatients may be more vulnerable to perceiving life stressors as traumatic and have "fewer psychological defences" and lower levels of resilience to manage these stressors.

Low openness in the TRD sample was positively associated with cooperativeness and reward dependence on the Temperament and Character Inventory (TCI) (Takahashi et al., 2013). The constructs of cooperativeness and reward dependence are self-reported styles of social behaviour. Individuals with low cooperatives are thought to be socially intolerant, disinterested in other people, alienated, hostile, unhelpful and revengeful (Balsamo, 2013). Furthermore, higher levels of social inhibition, as measured by the Social Inhibition (SI) Scale, have been associated with TRD (Crawford, et al., 2007). It has been suggested that socially inhibited individuals may not be able to create and maintain the social networks needed to moderate life stress and depression (Crawford, et al., 2007).

7.2.5 Hypotheses

RQ6: What is the underlying personality structure of depressed inpatients and is there an association between personality and TRD?

In line with previous research, it is hypothesised that the inpatient sample will have higher NEO-FFI Neuroticism scores and lower NEO-FFI extraversion scores compared to the externally sourced comparative samples. It is expected that personality ratings will be state related and Neuroticism will be associated with current psychological distress and symptom severity. There have been inconsistent reports of the association between the other NEO-FFI domains and depression and therefore no hypotheses were set for the inpatient sample.

In relation to TRD, the NEO-FFI domain of neuroticism is expected to be associated with higher levels of TRD as previously reported in medical scientific literature. Beyond neuroticism there is no clear evidence supporting the association between other NEO-FFI domains and TRD. Due to this no additional hypotheses were defined and the examination of the association between personality and TRD will be exploratory. However despite the exploratory nature of this analysis, it is expected that specific personality traits or patterns of personality will be predictive of TRD in the inpatient sample.

7.3 Methods

7.3.1 Methodology and measures. The methodology and sample have been described in Chapter Five and Six.

7.3.2 Informants. As mentioned in Chapter Five, participants were asked to nominate an informant who knew them when they were not depressed. Unlike participants who rated their personality whilst they were depressed, informants completed the informant version of the NEO-

FFI and were asked to "consider the personality of their friend or relative when they were well". Nominated informants were required to have known the participant for at least 10 years. This approach presumes that the participants had a period of wellness during the past 10 years. Due to the high levels of lifetime chronicity in the sample it is possible that informants were not rating pre-morbid personality but the participants' personality after the onset of depression. Comparing informant and self-rated personality can determine the stability of personality over time but may not be generalizable to premorbid functioning.

A response rate of 28.6% (N = 20) was achieved. The response rate was low as only 48 (68.6%) participants nominated an informant and only 20 (41.7%) of these nominated informants returned the questionnaire to the researcher. The majority of informants were female (N = 14; 70%). On average, informants had known the participants for 27.3 years (SD = 12.3 years). Informants were related to the participants in the following ways: partner/spouse (N = 7; 35%); parent (N = 8; 40%); adult child (N = 2; 10%); sibling (N = 2; 10%); or friend (N = 1; 5%).

7.3.3. Statistical analysis. All statistical analyses and figures were executed in Stata 12 (StataCorp LP, 2011). Unpaired t-tests were used to compare the means of the inpatient sample to the informant and comparative samples. Unpaired t-tests were used as the data were drawn from independent samples (informants vs. patients vs. comparative samples). Mann-Whitney U tests and pairwise correlations were used to assess differences in the inpatient sample on several variables of interest. Ordinary least squares (OLS) regression models were used to determine whether personality variables predicted current psychological distress and TRD. All data presented in the tables are raw NEO-FFI scores. Please see **section 6.3.3 TRD Index** for information related to the creation of the TRD composite index.

7.4 Results

7.4.1. Self- vs. informant ratings of personality. The means, standard deviations and unpaired t-tests between self- and informant-rated dimensions of the NEO-FFI are provided in Table 7.2. There were no significant differences between the means of self and informant ratings of the five NEO-FFI dimensions. This provides some reassurance that self-rated personality in these chronically and severely depressed inpatients are likely to be valid and stable over time. It can also be inferred that self-reported ratings of personality in the inpatient sample are not likely to be influenced by current depressed state and may be trait related or a scar-effect due to the high levels of chronicity in the sample.

Table 7.2

Self vs. informant ratings of the five dimensions of the NEO-FFI

	Self N = 20		Informant N = 20		Self vs. informant ratings
Domain	Mean ± SD	Range	Mean ± SD	Range	t-test
N	44.85 ± 7.52	27 – 57	43.00 ± 10.41	22 – 59	t(38) = .64, p = .523
E	32.65 ± 6.05	19 – 42	34.05 ± 9.90	17 – 47	t(38) = .54, p = .593
O	40.35 ± 6.66	30 – 54	40.50 ± 6.72	30 – 51	t(38) = .07, p = .944
A	43.90 ± 4.54	37 – 53	44.45 ± 5.78	34 – 54	t(38) = .33, p = .740
C	41.05 ± 5.18	31 – 53	41.90 11.05±	22 – 58	t(38) = .31, p = .747

N, Neuroticism; E, Extraversion; O, Openness to experience; A, Agreeableness; C, Conscientiousness

Table 7.3

NEO-FFI domains by gender and chronicity in the inpatient sample

	Male N = 19		Female N = 51			Chronic N = 64		Non-chronic N = 6		
Domain	Mean ± SD	Range	Mean ± SD	Range	Mann Whitney U Test	Mean ± SD	Range	Mean ± SD	Range	Mann Whitney U Test
N	44.05 ± 7.91	27 – 57	47.25 ± 6.55	27 – 55	z(68) = 1.62, p = .105	47.33 ± 6.08	32 - 58	36.33 ± 9.16	27 - 48	z(68) = -2.76, p <.005
E	30.79 ± 8.22	19 – 44	30.88 ± 6.21	19 – 47	z(68) = .02, p = .984	30.41 ± 6.41	19 - 47	35.67 ± 9.00	20 - 43	z(68) = 1.81, p = .071
O	37.53 ± 6.69	28 – 54	39.96 ± 6.09	29 – 52	z(68) = .91, p = .365	38.67 ± 6.42	28 - 54	37.50 ± 4.09	34 - 46	z(68) = -.46, p = .643
A	41.58 ± 4.66	31 – 47	42.75 ± 4.72	33 – 53	z(68) = .54, p = .592	42.44 ± 4.79	31 - 53	42.33 ± 3.93	38 - 49	z(68) = -.17, p = .866
C	41.58 ± 7.35	31 – 55	38.18 ± 6.89	24 – 53	z(68) = -1.82, p = .069	38.92 ± 7.22	24 - 55	41.00 ± 6.29	35 - 52	z(68) = .61, p = .542

N, Neuroticism; E, Extraversion; O, Openness; A, Agreeableness, C, Conscientiousness

Table 7.4

Correlation coefficients between current the NEO-FFI domains, symptom severity and current psychological distress in the inpatient sample (N = 70)

	N	E	O	A	C	HAM-D	K-10
N							
E	-.35**						
O	.09	.27*					
A	-.03	-.05	.05				
C	-.35**	.19	-.22	.12			
HAM-D	.07	-.33*	-.19	-.16	.11		
K-10	.23	-.40**	.07	-.09	.03	.33**	

** <.002; *<.05

HAM-D, 17-item Hamilton Depression Rating Scale; K-10, Kessler Psychological Distress scale; N, Neuroticism; E, Extraversion; O, Openness; A, Agreeableness, C, Conscientiousness

7.4.2. NEO-FFI domains and inpatient sample characteristics. There were no gender differences on the NEO-FFI domains (see Table 7.3). Current age was significantly correlated with conscientiousness (r(68) = .33, $p < .006$) but not with any other NEO-FFI domains (neuroticism, r(68) = -.13, $p = .283$; extraversion; r(68) = -.08, p = .505; openness r(68) = -.12, $p < .305$; agreeableness r(68) = .13, $p = .27$). Higher neuroticism was found in the inpatients with chronic illness duration (lifetime depression illness duration greater or equal than 2 years) compared to the inpatients with non-chronic illness duration (lifetime depression illness duration less than 2 years) (see Table 7.3).

Symptom severity and current psychological distress, as assessed with the HAM-D and K-10 respectively, were significantly negatively correlated with extraversion (see Table 7.4). After applying Bonferroni corrections only the negative association between current psychological distress and extraversion remained significant. Neuroticism was not found to be significantly correlated to current psychological distress or depression severity (see Table 7.4). This is could due to the abnormally high levels of both neuroticism (M= 46.4, SD = 7.03, median = 47) and current psychological distress (M = 35.3, SD = 4.9, median = 36) in the inpatient sample. The level of neuroticism in the inpatient sample is significantly higher than a comparative sample of people who have never been depressed (see Table 7.6). In addition, when reviewing the cut-offs for the Kessler

Psychological Distress Scale (K-10), on average the inpatient sample had a high level of psychological distress ranging from moderate to very high (19 to 44) . This confirms that the inpatient sample were reporting high levels of distress and neuroticism in comparison to normal population.

Using OLS regression with current psychological distress as the dependent variable and neuroticism as the only independent variable in the model, neuroticism just fails to reach significance, b = .16, t (69) = 1.99, p = .051. Although this association was not statistically significant, inspection of the two-way scatter plot (Figure 7.1) suggests that higher levels of current psychological distress may be associated with higher neuroticism scores. However, the expected relationship between neuroticism and current psychological distress may not be linear due to a ceiling effect on both variables (Figure 7.1). The ceiling effect was not as pronounced in depression severity scores (HAM-D) (Figure 7.1). This could be due to depression severity being clinician rated whereas both neuroticism and current psychological distress were self-reported.

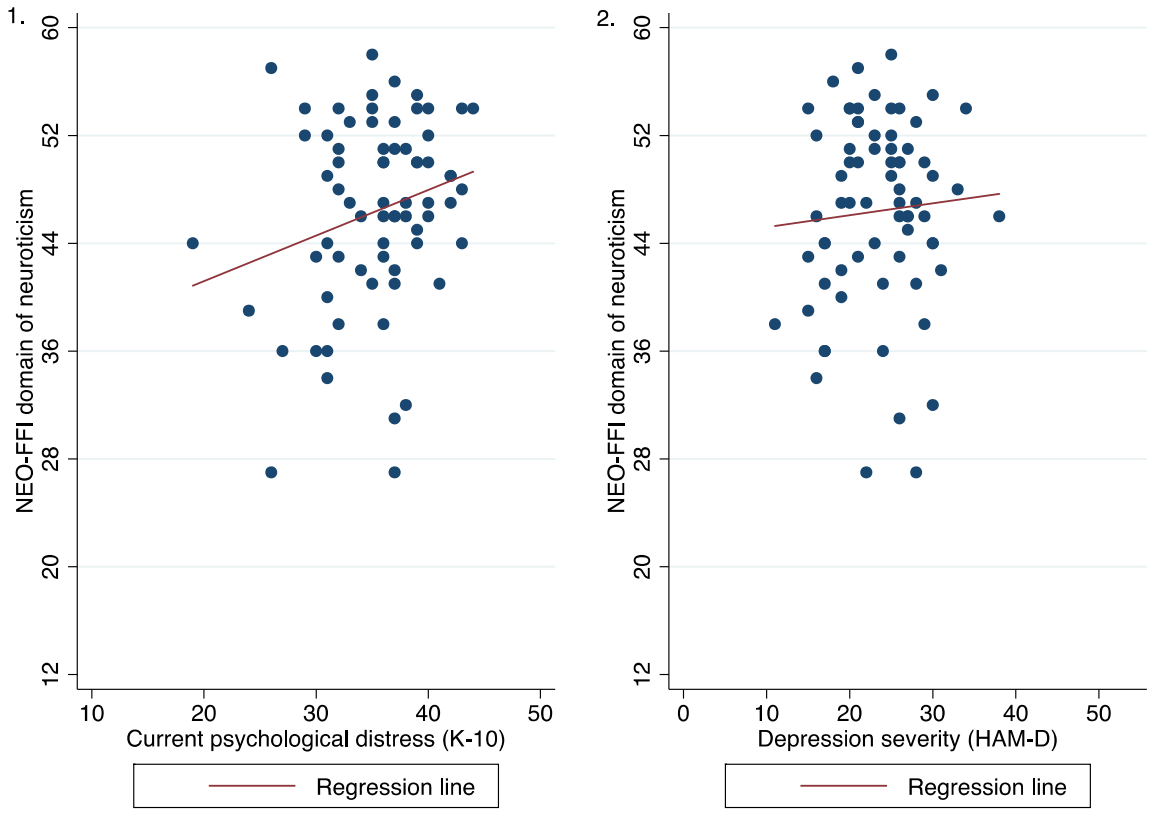


Figure 7.1. Scatter diagrams between NEO-FFI domain of neuroticism and: 1) depression symptom severity (HAM-D); 2) current psychological distress (K-10) in the depressed inpatient sample (N = 70)

When extraversion is added into an OLS regression model alongside neuroticism, extraversion is significantly correlated with current psychological distress, b = -.26, t (69) = -3.06, p < .003. This second model, which included neuroticism and extraversion, explained an extra 11% of the variance in current psychological distress compared to the model with neuroticism as the only predictor (Adjusted R^2= .041 to Adjusted R^2= .15). Extraversion emerges as an underlying predictor of current psychological distress rather than neuroticism most likely due to the ceiling effect of neuroticism. This finding was replicated for depression severity (HAM-D), with extraversion but not neuroticism being associated with depression severity in an OLS regression, b = -.27, t (69) = -2.83, p < .006.

The remaining three NEO-FFI domains are not significantly associated with current psychological distress when considered independently in OLS regression models (Openness, b = .56, t (69) = .59, p = .558; Conscientiousness, b = .02, t (69) = .29, p = .774; agreeableness, b = -.09, t (69) = -.70, p = .483). However when all five NEO-FFI domains are combined together in a OLS regression model predicting current psychological distress, extraversion maintains its significance as a predictor (b = -.34, t (64) = -3.87, p < .001) and openness (b = .19, t (64) = 2.11, p < .039) and conscientiousness (b = .17, t (64) = 2.02 p < .048) emerge as significant predictors of current psychological distress. When compared to the model with only neuroticism and extraversion (Adjusted R^2= .15), the addition of the three remaining NEO-FFI domains explain an extra 5% of the variance in current psychological distress (Adjusted R^2= .20). This suggests that extraversion is the most useful predictor of current psychological distress but openness and conscientious also contribute to the association between personality and current psychological distress in the inpatient sample.

Likewise, extraversion, but no other NEO-FFI domain, was negatively associated with a lifetime suicide attempt in the inpatient sample (see Table 7.5). Over half the inpatients in the sample had attempted suicide at least once during their lifetime (N = 41; 58.6%). A logistic regression model was performed with the five NEO-FFI personality domains as predictors of a lifetime suicide attempt controlling for age and current psychological distress. The goodness-of-fit of the multivariate model was tested with the Hosmer-Lemeshow statistic and was found to be satisfactory (χ^2 = 1.93; df = 8; p =.983). Lower levels of extraversion significantly predicted a lifetime suicide attempt in the inpatient sample, OR = .90 (95% CI .81 – 1.00) (see Table 7.5). Thus, extraversion emerges as a potentially useful personality predictor of both current psychological distress and a lifetime suicide attempt.

Table 7.5

Multivariate logistic regression model predicting lifetime suicide attempt

Predictor	OR	CI (95%)	z	p
N	1.07	.97- 1.17	1.36	0.173
E	.90	.81 - 1.00	-1.96[a]	<.050
O	.97	.88 - 1.07	-.53	.595
A	.98	.87 – 1.10	-.31	.759
C	1.05	.96 - 1.14	1.06	.288
K-10	.98	.86 - 1.12	-.28	.779
Current age (in years)	.97	.93 – 1.01	-1.63	.103

OR, odds ratio; CI, confidence interval; K-10, Kessler Psychological Distress scale; N, Neuroticism; E, Extraversion; O, Openness; A, Agreeableness, C, Conscientiousness

Coding: lifetime suicide attempt (1.00) no lifetime suicide attempt (0.00)

[a] Significant finding

Table 7.6

Inpatient sample vs. never depressed and depression in remission samples on the NEO-FFI domains

NEO-FFI domains	Inpatient sample N = 70	NESDA never depressed sample[a] N = 990	NESDA depression in remission sample[a] N = 585	Inpatient vs. NESDA never depressed sample[a]	Inpatient vs. NESDA depression in remission sample[a]
	Mean ± SD			t-test	
N	46.39 ± 7.03	27.50 ± 7.10	33.40 ± 7.10	t(1058) = 21.53, p <.001	t(653) = 14.48, p < .001
E	30.86 ± 6.75	41.10 ± 6.20	37.80 ± 6.60	t(1058) = 13.27, p <.001	t(653) = 8.29, p < .001
O	38.57 ± 6.25	37.00 ± 5.10[b]	36.60 ± 5.30	t(1057) = 2.45, p <.015	t(653) = 2.88, p < .004
A	42.43 ± 4.70	45.50 ± 4.80	44.60 ± 5.40	t(1058) = 5.18, p <.001	t(653) = 3.22, p <.001
C	39.10 ± 7.12	44.80 ± 5.30	42.80 ± 5.70	t(1058) = 8.48, p <.001	t(653) = 4.99, p <.001

N, Neuroticism; E, Extraversion; O, Openness to experience; A, Agreeableness; C, Conscientiousness

[a]Karsten, Penninx, Riese, Ormel, Nolen, and Hartman, 2012

[b]Due to missing data on the NEO-FFI domain of Openness the sample size = 989

7.4.3. NEO –FFI: inpatient sample vs. comparative samples. As it was not feasible to recruit a parallel control group, data on comparative samples were sourced from the literature. Means, standard deviations and sample sizes of the NEO-FFI domains were retrieved from a published study (Karsten et al., 2012). The NEO-FFI domain scores for the inpatient sample were compared to two externally sourced samples: never depressed controls and people with depression in remission. Both comparative samples were retrieved from Karsetn et al., (2012) and are subsamples from the Netherlands Study of Depression and Anxiety (NESDA), an 8-year cohort study investigating the predictors and course of depression and anxiety (Karsten, Penninx, Riese, Ormel, Nolen, & Hartman, 2012). The total sample consisted of 2,981 participants ranging in age from 19 to 70 years (M = 41.9 years; SD = 13.1 years) of whom 33.6% were male. The sample was recruited from the community (N = 564), primary care settings (N = 1,610) and mental health organisations (N = 807). There was a 12.9% attrition rate from baseline to the 2-year follow-up period resulting in 2,596 participants included in follow-up analyses.

Data from the NESDA which used a translated version (English – Dutch) of the NEO-FFI were the only comparative data available at this time. There are cultural differences between Australia and the Netherlands that cannot be ignored including national character, history and language. However, the Personality Profiles of Cultures (PPOC) Project found that the FFM generalises across cultures (N = 50) and that the factor structure of the FFM is maintained and replicated in all cultures tested (McCrae et al., 2005). The findings from this project conclude that personality structures are universal, can be compared across cultures and are not related to national character stereotypes (Terracciano & McCrae, 2006). Although, an Australian comparative sample would have been preferable, the evidence suggests that the NESDA sample is a valid comparator.

The NESDA study assessed the presence of depressive or anxiety disorders at baseline and at 2-year follow-up using the WMH-CIDI. The depression in remission subsample (N = 585) consisted of individuals who had a depressive disorder (Major Depressive Disorder and/or Dysthymia) at baseline but no depressive disorder at 2-year follow-up. The never depressed controls (N = 990) consisted of individuals who had no depressive or anxiety disorder at baseline and no depressive or anxiety disorder at the 2-year follow-up. Table 7.7 displays the baseline characteristics of the comparative samples and compares them to the inpatient sample. There were no significant differences in the gender ratio between the three samples (X^2 (2) = 1.33, p = .514) but there was a significant effect of age where the depression in remission sample were slightly younger than then the never depressed and inpatient sample (F (2, 2037) = 4.23, p < .015).

Table 7.7

Characteristics of the never depressed, depression in remission and inpatient samples

Characteristic	Inpatient sample N = 70 (%); Mean ± SD	NESDA never depressed [a,b] N = 1454 (%); Mean ± SD	NESDA depression in remission [a,b] N = 516 (%); Mean ± SD
Gender			
Males	27.1	34.8	32.4
Females	72.9	65.2	67.6
Age (years)	42.0 ± 14.2	42.3 ± 13.7	40.3 ± 12.5

[a] Karsten et al., 2012

[b] Only baseline characteristics were available

An identical pattern of personality differences emerged when comparing the inpatient sample to the NESDA never depressed and depression in remission samples using unpaired t-tests (see Table 7.6). In comparison to both NESDA samples, the inpatient sample had significantly higher scores on the neuroticism and openness domains, and significantly lower scores on the extraversion, agreeableness and conscientiousness domains. Figure 7.1 visually displays the differences between the samples and depicts the stronger effect between the NESDA never depressed sample and the inpatient sample.

The mean neuroticism score in the inpatient sample was elevated two standard deviations above the NESDA never depressed neuroticism sample mean. Assuming that the NESDA never depressed sample is normally distributed, approximately 0.5% of individuals who have never been depressed would have neuroticism scores as high as the inpatient sample mean neuroticism score. In contrast, extraversion scores in the inpatient sample were approximately one and half standard deviations below the NESDA never depressed extraversion sample mean. When neuroticism and extraversion are viewed together in comparison to the NESDA never depressed and depression in remission samples, the inpatient sample reflects the well-established association between high neuroticism and low extraversion found in depression. The same effect of higher neuroticism and lower extraversion was reported in the NESDA depression in remission sample in comparison to the NESDA never depressed sample (Karsten et al. 2012) but not to the same degree as found in the inpatient sample compared to the NESDA never depressed sample.

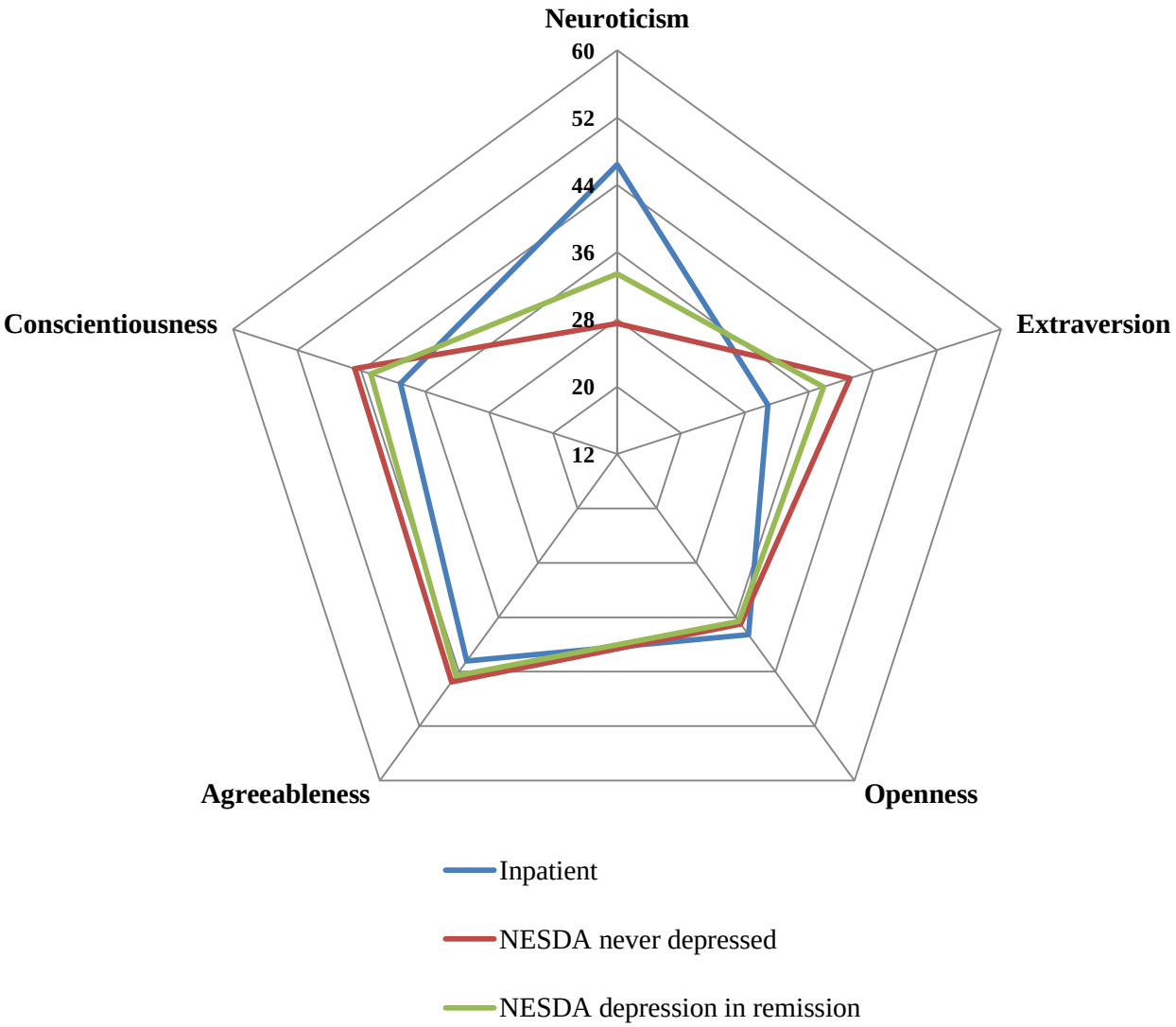


Figure 7.2. Visual representation of the mean NEO-FFI domain scores for the inpatient sample, NESDA never depressed and NESDA depression in remission sample (Karsten, Penninx, Riese, Ormel, Nolen & Hartman, 2012).

7.4.5. Predicting TRD using personality domains. Two OLS regression models were used to investigate whether specific personality domains or patterns of personality predicted TRD. In line with the TRD predictive model (Chapter Six, see Table 6.7), variables used to rate TRD in staging models such as symptom severity (as measured by the HAM-D), number of antidepressant treatments, duration of illness and treatment strategies (i.e. ECT and augmentation) were not added to the OLS models due to multicollinearity with the TRD index. In order to combat the effect of current mood state on personality, current psychological distress was added as a controlling variable in both models.

The first model examined the predictive utility of the NEO-FFI domains on the TRD index controlling for age, gender and current psychological distress (see Table 7.8). The second model combined only features that were thought to be predictors (e.g. family history, age) not consequences (e.g. suicide attempts, cognitive functioning) of TRD, alongside any significant NEO-FFI personality domains from the first model (see Table 7.8).

7.4.6. Personality domains only model. The personality model with TRD index as the outcome variable was performed with all five NEO-FFI domains as predictors controlling for age, gender and current psychological distress. An interaction between neuroticism and extraversion was not significant and was not included in the model. The only significant predictor of TRD was the NEO-FFI domain of openness (see Table 7.8). Lower openness was predictive of higher levels of TRD when all other variables in the model were held constant, b = -.20, t (69) = -2.17, p <.034. The model was significant (F (8, 61) = 2.13, p < .046) and explained 12% of the variance in the TRD index (adjusted R^2 = .12). The controlling variables, age, gender and current psychological distress were not significant. There was no evidence of multicollinearity between the predictors as determined by a mean variance inflation factor (VIF) of 1.35 with tolerance levels greater than 0.1. A White test (χ^2 = 39.52, p = .623) found no presence of heteroscedasticity indicating that the variance of errors are constant and the model was specified correctly.

7.4.7. TRD predictive model with the NEO-FFI domain of openness. In this model, the NEO-FFI domain of openness, which was a significant predictor of TRD in Model 1, was added to the following variables: age, gender, education, current psychological distress, age of onset, family history, childhood sexual abuse, medical and psychiatric comorbidity (see Table 7.8). When all five NEO-FFI domains were added alongside the predictor variables to predict the TRD index the regression model was not significant, F(13, 56) = 1.76, p <.073. Therefore only the NEO-FFI domain of openness was added to the predictive model (see Table 7.8).

Model 2 explained an extra two percent of variance in TRD index scores compared to the personality only model (adjusted R^2 = .14 versus adjusted R^2 = .12, respectively). Openness maintained its significance as a predictor in the model. Lower levels of openness was found to predict higher levels of TRD when all other variables in the model were held constant, b = -.71, t (69) = -2.07, p <.042. In addition, an earlier age of onset age was found to predict higher levels of TRD when all other variables in the model were held constant, b = -.12, t (69) = 2.20, p <.032. The predictive TRD model with the NEO-FFI openness domain was significant F(10, 59) = 2.09, p <.040. There was no evidence of multicollinearity between the predictors as determined by a mean variance VIF) of 1.38 with tolerance levels greater than 0.1. Additionally, a White's test (χ^2 = 61.26, p = .503) found no presence of heteroscedasticity indicating that the variance of errors are constant and the model was specified correctly.

Table 7.8. *OLS regression models predicting TRD index*

	Model 1: Personality domains only					Model 2: Personality and predictive features				
Predictors	b	Standard error	t	95% CI	p	b	Standard error	t	95% CI	p
Age (years)	.07	.04	1.66	-.01-.14	.101	.12	.05	1.97	-.00-.22	.054
Gender										
Female	*Reference category*					*Reference category*				
Male	-2.13	1.23	-1.74	-4.59- .32	.087	-2.04	1.22	-1.67	-4.49-.40	.100
K-10 score	-.07	.13	-.57	-.32-.18	.568	-.13	.11	-1.21	-.35-.09	.229
N	.05	.08	.59	-.12-.22	.559					
E	.00	.10	.00	-.20-.20	.998					
O	-.20	.09	-2.17	-.39- -.02	< .034	-.17	.08	-2.07	-.34--.01	<.042
A	.16	.11	1.36	-.07-.03	.178					
C	-.14	.09	-1.61	-.32-.03	.113					
Age of onset (years)						-.12	.06	-2.20	-.23--.01	<.032
Reported childhood trauma						-.92	1.15	-.80	-3.22-1.38	.425
Education										
High school/skilled vocation						*Reference category*				
Tertiary						-1.02	1.18	-.87	-3.38-1.33	.389
Number of 1st degree family members with depression						-.09	.60	-.14	-1.28-1.11	.887
Number of lifetime DSM-IV Axis I co-morbid psychiatric disorders						.54	.44	1.24	-.33-1.42	.219
Number of co-morbid medical conditions						.46	.49	.94	-.53-1.45	.353
	Model Adjusted R^2 = .12					Model Adjusted R^2 = .14				

N, Neuroticism; E, Extraversion; O, Openness to experience; A, Agreeableness; C, Conscientiousness; K-10, Kessler Psychological Distress Scale; HVLT, Hopkins Verbal Learning Test

7.5. Discussion

The aim of the current study was to determine whether depressed inpatients have a unique personality profile as measured by the NEO-FFI and whether specific personality structures are associated with treatment resistance. It has been repeatedly debated whether high scores on personality domains in clinical populations represent a temporary state effect or are a valid reflection of enduring personality function (Ormel, Riese, & Rosmalen, 2012). In order to reduce the influence of the current depressed state on personality measurements, many studies are employing informant ratings of personality (Bagby, Rector, Bindseil, Dickens, Levitan, & Kennedy, 1998). The use of informant data can improve the reliability and validity of the personality assessment. However, caution is warranted as informants provide only one perspective and do not have direct access to the thoughts and feelings of the person they are rating (Klonsky & Oltmanns, 2002). If the ratings between self and informants are divergent then one source of information, either the participant or the informant, needs to be deemed more valid.

In the current study, to assess whether personality ratings made by the inpatients were dependent on their current depressed state, the inpatients' self-reported personality ratings were compared to informant ratings of the inpatients' personality. No significant differences between the means of the self ratings and informant ratings on the five NEO-FFI domains were found. In order to investigate the influence of the participants' current state on their self-reported personality ratings, I compared current psychological distress, as measured by the K-10, to the five dimensions of the NEO-FFI. Importantly, only modest correlations were found between the five NEO-FFI domains and current psychological distress. The relationship between current psychological distress and the NEO-FFI domains are discussed in a forthcoming section. Participant ratings of personality appeared valid and not dependent on their current depressed state. However, it remains possible that both informant and participant ratings of personality were state dependent as the majority of the inpatient sample had a chronic illness duration defined as a depressive illness duration greater than two years (N= 64; 91.4%). Thus, despite asking informants to rate the personality of participants when they were well it is possible that due to the chronicity of the participants' depression, informants may not be able to accurately recall the participants' pre-morbid personality. This incorrect perspective of participants' pre-morbid personality could be the result of cognitive and environmental embedding in which experiences and long term exposure to the determinants of negative affect result in sustained changes in the beliefs about the self and this is in turn reflected in personality assessments (Ormel, Riese, & Rosmalen, 2012).

7.5.1 Personality structure of depressed inpatients. The depressed inpatients had a significantly different personality profile from the externally sourced comparative samples. When

compared to the never depressed and depression in remission samples the depressed inpatients had significantly higher scores on the neuroticism and openness domains and significantly lower scores on the extraversion, agreeableness and conscientiousness domains. In line with the current findings, Trull and Sher (1994) found the same pattern of personality functioning was characteristic of psychopathology. The inpatient sample had significantly higher neuroticism mean scores than the depression in remission sample which is supportive of previous findings indicating that neuroticism scores decrease in response to treatment (Bagby & Ryder, 2000; Knutson, et al., 1998; Tang, DeRubeis, Hollon, Amsterdam, Shelton, & Schalet, 2009). In the current study, neuroticism scores are significantly elevated in the depression in remission sample compared to the never depressed sample providing additional evidence that personality scores do not return to normal despite response to treatment, t (1573) = 15.93, p <.001. Although speculative, this suggests that a pervasive pattern of high neuroticism might represent a lasting 'scar' effect, where a permanent change in personality occurs. This notion is supported by the finding in the current study that neuroticism, but no other NEO-FFI domain, was associated with chronicity in the inpatient sample. However, this finding should be interpreted cautiously, as there was limited variability in illness course, with the vast majority of the inpatient sample having a chronic illness duration.

The depressed inpatient sample had a characteristic personality profile, which differed from the normal population and is likely reflective of maladaptive personality functioning. The majority of the depressed inpatients in the current sample were chronically depressed (91.4%) and unresponsive to at least two antidepressants (94%). The chronicity and poor response to treatment in the sample may be associated with high neuroticism. Psychotherapeutic treatment interventions should be aimed at these personality vulnerabilities as potential barriers to treatment response in patients with chronic and TRD.

7.5.2 Extraversion as a protective factor. The level of current psychological distress in the inpatient sample ranged from moderate to very high. Thus, the inpatient sample as a whole was highly distressed and neurotic compared to the normal population. The ceiling effect on both factors (current psychological distress and neuroticism) may explain the unexpected finding that neuroticism was not associated with current psychological distress. In an OLS regression model with neuroticism as the only predictor of current psychological distress the expected trend was present but not significant. When extraversion was added to the model it emerged as a useful predictor of psychological distress. A non-significant interaction between neuroticism and extraversion, and minimal predictive utility provided by the other three NEO-FFI domains (openness, agreeableness and conscientiousness) in predicting current psychological distress confirmed the importance of extraversion as a predictor of current psychological distress. The finding suggests that extraversion rather than neuroticism is the most significant predictor of current

psychological distress with depressed inpatients who report higher levels of extraversion also reporting lower levels of current psychological distress.

Extraversion, but no other NEO-FFI personality domain, was also found to be predictive of lifetime suicide attempts in a multivariate logistic regression model. Lower levels of extraversion predicted a lifetime suicide attempt in the depressed inpatient sample when controlling for the other NEO-FFI domains, age and current psychological distress (see Table 7.5). This in line with findings from a large systematic review (N = 90), which examined the link between personality and suicidal ideation, suicide attempts and suicide completions (Brezo, Paris & Turecki, 2006). Lower levels of extraversion were associated with suicide attempts regardless of age in the review (Brezo, Paris & Turecki, 2006). Along with low levels of extraversion, the review also highlighted the strong relationship between feelings of hopelessness and high levels of neuroticism in suicide attempts and completions (Brezo, Paris & Turecki, 2006). In the current study, the inpatient sample were found to be highly neurotic and highly distressed with over half the sample having attempted suicide at least once during their lifetime. With this in mind it would seem the majority of the sample would be at risk of suicide and thus identifying factors which protect against suicidal behaviour in this vulnerable population is crucial. The personality domain of extraversion and features associated with high extraversion may provide insight into the protection against suicidal behaviour.

It is an established feature of personality functioning that extraversion is associated with resilience, coping and happiness (Campbell-Sills, Cohan & Stein, 2006; Costa & McCrae, 1980; Lucas & Fujita, 2000; Riolli et al., 2002). In previous studies, extraversion has been positively related to both happiness (Costa & McCrae, 1980; Lucas & Fujita, 2000; Strack et al., 1991) and resilience (Campbell-Sills, Cohan & Stein, 2006; Riolli et al., 2002). In turn, neuroticism has a strong negative association with both happiness and resilience (Campbell-Sills, Cohan & Stein, 2006). Resilience refers to the "dynamic process wherein individuals display positive adaption despite experiences of significant adversity or trauma" (Luthar & Cicchetti, 2000 pp.858 cited in Campbell-Sills, Cohan & Stein, 2006). Extraversion and resilience are thought to be highly related because both are associated with positive emotions and increased sociability and social support (Campbell-Sills, Cohan & Stein, 2006). A positive affect together with social support is considered to buffer the effects of stress and adversity in resilient individuals (Campbell-Sills, Cohan & Stein, 2006). Therefore, given the strong relationship between extraversion and resilience, it is unsurprising that higher levels of extraversion protect against self-reported psychological distress and lifetime suicide attempts in the inpatient sample.

7.5.3 Predictors of treatment resistance in depressed inpatients. The depressed inpatients as a group had higher levels of openness to experience compared to the never depressed and depression in remission samples. Examination of the inpatient sample on its own found that higher

levels of treatment resistance, as measured by the TRD index, was associated with lower levels of openness to experience. However, the lower levels of openness to experience found in relation to TRD are still higher than what would be found in normal population. Therefore the role that openness to experience plays in treatment resistance is likely to involve phenomena associated with abnormally high levels of openness.

The openness to experience domain is the personality domain least associated with psychopathology and is considered to underpin imagination, creativity and intelligence (Duberstein, 2001; Williams, Rau, Cribbet, & Gunn, 2009; Piedmont, Sherman, & Sherman, 2012). Dysfunctional levels of high openness to experience, as represented in the depressed inpatient sample, are thought to result in a preoccupation with fantasy and daydreaming, eccentric thinking, unstable goals and oddity (Widiger, Costa Jr, & McCrae, 2002). An alternative explanation may be that high openness to experience is linked to a higher level of education and/or intelligence in the depressed inpatient sample compared to normal population. According to the Australian Bureau of Statistics (ABS) in May 2014, 16% of Australians aged between 15 and 74 years were tertiary educated. The rate of tertiary education in the inpatient sample (N = 23; 32.8%) is double the national rate indicating that the inpatient sample were more educated than the general population and this may explain the high levels of openness to experience found in the inpatient sample.

When socio-demographic and clinical features were added into the model along with NEO-FFI domains, openness to experience maintained its significance as a predictor after controlling for education status (high school/vocation education vs. tertiary education). Thus the relationship between the personality domain of openness and treatment resistance may be associated with other facets of high openness rather than reflective of higher education. Disconnection from social groups is representative of maladaptive levels of high openness due to odd and eccentric characteristics, which may not be easily understood or tolerable by others (Piedmont, Sherman, & Sherman, 2012). High openness traits can become dysfunctional when they develop as compensatory behaviours for trauma, loneliness and isolation (Lynn & Ruhe, 1988). An earlier study identified higher social inhibition, lower perceived social support and higher rates of social phobia in TRD (Crawford, Parker, Malhi, Mitchell, Wilhelm, & Proudfoot, 2007). Therefore personality structures, which are indicative of social isolation, loneliness and low social support, may contribute to the development and maintenance of treatment resistance. Alternatively, social isolation may be a consequence of the isolating nature of a chronic illness and the stigma surrounding mental illness, which results in self and/or community isolation.

The integrated regression model, which combined socio-demographic, clinical predictors and the NEO-FFI domain of openness explained 14% of the variance in the TRD index. Alongside the personality domain of openness, an earlier age of onset was also found to predict higher levels

of TRD (see Table 7.8). An earlier age of onset was identified in the 2007 NSMHWB (Chapter Four) as a risk factor for chronic depression and also in an OLS regression model investigating the correlates of TRD (Chapter Six). Due to the highly specific sample, the finding that the personality domain of openness is associated with TRD cannot be generalised to chronic depression and individuals who are non-responsive to treatment in the community. However, a personality profile of high neuroticism and openness domains together with low extraversion, agreeableness and conscientiousness domains may predict a more chronic illness course and poorer response to treatment in individuals with depression.

7.5.4 Conclusion

The current study investigated the underlying personality structure of a sample of depressed inpatients rated with TRD. In line with previous findings, a NEO-FFI personality profile of high neuroticism and openness domains together with low extraversion, agreeableness and conscientiousness was found. This particular NEO-FFI profile has been associated with psychopathology in medical scientific literature (Trull & Sher, 1994). When personality factors were added to an OLS model predicting TRD, personality factors did not explain any additional variance in TRD index scores and none of the personality factors significantly predicted TRD.

The present study is limited by its use of referred inpatients and its use of external comparative samples. However, convergent self and informant ratings of personality suggest a long-term scar effect of severe, chronic, depression or a life-long pervasive pattern of maladaptive personality structures in depressed inpatients. The assessment and identification of maladaptive personality structures may provide greater insight into role of personality in treatment response and may guide towards more appropriate treatment strategies.

Chapter Eight

Conclusion

8.1 Introduction

The purpose of this final chapter is to summarise and integrate the main findings of the thesis and to discuss the clinical implications and future directions of this research. This thesis has reviewed the conceptualisation and identification of chronic and treatment resistant depression using multiple research methods including systematic reviews and the analysis of primary and secondary data. A conceptual funnel approach was applied to this thesis. The thesis began very broadly by systematically reviewing medical scientific literature on the concept of TRD (Chapter Two), the following empirical chapter attempted to identify chronic and treatment-resistant depression in the Australian community using data from the 2007 NSMHWB (Chapter Four) and the final empirical chapters assessed the degree of chronicity and treatment resistance in a sample of depressed inpatients (Chapter Six and Seven). Two methods chapters (Chapter Three and Five) were provided outlining the research methodology for the 2007 NSMHWB and the inpatient data presented in the final two empirical chapters.

8.1.1 Summary of thesis. The introductory chapter (Chapter One) provided an overview of the concept of clinical depression and the burden associated with a chronic and unremitting illness. The phenomenon of non-response to treatment was introduced and was implicated as a potential source of the large disease burden posed by depression. Treatment resistance has become increasingly relevant since the STAR*D study reported relatively modest response and remission rates in depressed outpatients treated with antidepressants (Gaynes, Warden, Trivedi, Wisniewski, Fava, & Rush, 2009). The point was made that there is no clear understanding or consenus on what consitutes TRD and how patients might become resistant to treatment. Many prominent researchers have discussed their dissatisfaction with current terminology and lack of progress in identifying why some patients are resistant to treatment while others are not (Berlim & Turecki, 2007; Parker, 2005; Sourey, 2007 cited in Moller et al., 2013). Furthermore, the medical scientfic literature on TRD has been largely focused on treatment strategies for these patients and has not been able to identify phenotypes that might be characteristic of TRD (Moller et al, 2013). Thus, the natural starting point of the thesis was to review how TRD is current currently conceptualised in medical scientific literature and how it is indentified in clinical practice (Chapter Two).

I next provided an overview of the 2007 NSMHWB research methodology (Chapter Three) and utilsed these data in an attempt to identify community-residing individuals with chronic and treatment-resistant depression (Chapter Four). The survey was not able to identify individuals with TRD due to a lack of historical treatment data. However, community-residing individiuals with

chronic depression were identifiable. The 2007 NSMHWB provided the first opportunity to report epidemiological data on the new conceptualisation of chronic depression as Persistent Depressive Disorder (see Chapter Four and Murphy & Byrne, 2012). There is considerable conceptual overlap between TRD and chronic depression particularly in Western societies in which people have relatively good access to healthcare. It is also likley that a proportion of individuals with chronic depression may be untreated and self-manage their depression. In the 2007 NSMHWB it was possible to identify differences in health services utilisation among chronically depressed individuals in the Australian community (Chapter Four). Differences in health service utilisation in individuals with chronic depression may provide greater understanding into the phenomenon of TRD, as a higher level of health service utilisation may indicate TRD, particularly in indidviuals who have been hospitalised for their depression (Chapter Four).

However, it is only possible to examine the conceptual overlap between chronic and TRD in situations in which individuals have been continuously in treatment. As I highlighted in Chapter Four using the 2007 NSMHWB and in line with previous evidence (Draper & Low, 2009), it was evident that higher-level treatment settings such as tertiary care settings are likely manage patients with TRD. Therefore in Chapters Six and Seven, I assessed the degree of chroncity and treatment resistance in a sample of depressed inpatients. Recruiting a sample of depressed inpatients provided the opportunity to compare the available staging models of TRD (see section *1.9.5 Staging models of TRD*). The sample of depressed inpatients was rated on each available staging model and the relationship between the models was reported. The high inter-relatedness between the models indicated that each model was likely measuring the same underlying concept. In order to capture all the variability in the models, a composite index of TRD was created. The newly created TRD index was used to determine what factors were associated with a higher level of TRD and whether rating TRD on a continuum provide greater understanding of the phenomenon, above and beyond what is provided by a dichotomous definition of TRD as the failure of three or more antidepressants.

The newly created index of TRD was also used to assess whether higher levels of TRD are associated with particular personality structures (Chapter Seven). The role personality plays in TRD has been understudied. The personality structure of the depressed inpatient sample was compared to the personality structure of externally sourced comparative samples of never depressed individuals and individuals with depression in remission. The depression in remission sample was chosen to represent depressed individuals who are treatment responsive. A characteristic personality profile was found for the depressed inpatients compared to the control samples. A more complicated regression model combining socio-demographic characteristics, clinical features (see Chapter Six) and the personality profile unique to the depressed inpatients was performed to determine whether personality contributes to the phenomenon of TRD.

8.2. Conceptualisation of Chronic and Treatment-resistant Depression

8.2.1 Prevalence of chronic and treatment-resistant depression. As emphasised in the introduction and Chapter Two, the prevalence of TRD has proven difficult to estimate. This is because prevalence estimates of TRD are dependent on the definition and research methods used to identify the phenomenon, as well as access to effective treatment services. These factors vary widely between studies and result in difficulty comparing and accurately reporting the phenomenon. The STAR*D study found that non-remission and treatment resistance were a common occurrence in the depressed outpatients participating in the trial (see *1.10.1 STAR*D*). Likewise, there was a high rate of antidepressant treatment failure in the depressed inpatient sample I recruited (see Chapter Five, Six and Seven). Approximately 75% of the inpatient sample (N = 54) had failed three or more antidepressants with the vast majority of the sample (N = 66; 94%) failing at least one or two antidepressants. When TRD is rated on a continuum, the depressed inpatient sample had moderate to high level of TRD as rated by the available staging models (see *5.4.7 Treatment resistance*).

The high prevalence of TRD in inpatient settings is likely due to individuals with multiple treatment failures seeking or requiring higher level health services. Differences in service utilisation in individuals with depression can be due to variations in service access, perceived need for services, treatment-seeking behaviour and illness characteristics better suited to a particular service. Illness characteristics, such as greater symptom severity, co-morbidity, treatment resistance and risk to self or others may result in higher specialty care such as hospitalisation. In line with this notion, rates of public and private psychiatric hospitalisations in Australia between 1998 to 2005 reported in the Australia's National Morbidity Database, were higher in individuals diagnosed with an ICD-10 severe depressive disorder (without psychosis) compared to individuals diagnosed with a less severe form of ICD-10 depressive disorder (mild or moderate) (see *1.8 Treatment Settings in Australia*) (Draper & Low, 2009). Using data from the 2007 NSMHWB, I assessed differences in health service utilisation amongst individuals in the Australian community with chronic depression (Chapter Four). In line with the findings from Draper and Low (2009), I found that individuals with chronic depression who accessed higher levels of health service utilisation (e.g. tertiary care) had more complex clinical presentations, suggesting treatment resistance. Three levels of health service utilisation in chronically depressed individuals were compared: 1) primary care; 2) tertiary care; and 3) untreated. Unsurprisingly, chronically depressed individuals in tertiary care had a greater number of episodes of depression, more severe symptoms, a greater family history of depression, higher levels of psychiatric co-morbidity, a greater traumatic load, higher levels of disability and higher levels of current psychological distress in comparison to chronically depressed individuals treated

in primary care or who were untreated. The findings from the 2007 NSMHWB support the notion that inpatient mental health services are more likely to treat patients with TRD (Chapter Four).

Subsequently, it was not unexpected to find a high prevalence of chronicity in the depressed inpatient sample (Chapter Six). The majority (91.4%) of depressed inpatients studied had a lifetime depressive illness duration greater than two years, indicating a chronic illness trajectory. This is understandable given the above discussion on the utilisation of psychiatric hospitalisation and findings from the STAR*D study which reported chronicity as a common feature of treatment resistance in depressed outpatients (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Community-based longitudinal studies on the course of depression, report between 15 and 24.5% of depressed individuals maintain a chronic illness course during a follow-up period (Penninx, et al., 2011; Eaton, Shao, Nestadt, Lee, Bienvenu, & Zandi, 2008; Spijker, de Graaf, Bijl, Beekman, Ormel, & Nolen, 2002). In comparison, we found that chronic depression was present in 29.4% of Australian community-residing individuals in the cross-sectional 2007 NSMHWB survey diagnosed with a lifetime depressive disorder (DSM-IV Dysthymic Disorder or MDD) (Murphy and Byrne, 2012).

Despite the obvious relationship between chronicity and TRD, both can exist without the other. A proportion of community-residing chronically depressed individuals (16.6%) were found to be untreated and self-manage their depression (Chapter Four). Untreated chronically depressed individuals in the 2007 NSMHWB were more likely to be male, have a later age of onset and an older current age. They also had less complex presentations (in terms of co-morbidity and traumatic load) and were less disabled and less psychologically distressed compared to the chronically depressed individuals who had received treatment (Chapter Four). Without treatment or medical intervention these individuals are excluded from TRD criteria despite having a chronic illness duration. Furthermore, it is possible within a 12-month period, to fail two or even three or more adequate antidepressant trials of at least 6 weeks' duration. Thus, TRD can be designated without chronicity, just as chronicity can be designated without TRD. At the present time, when TRD is most commonly defined as the failure of two antidepressants, the phenomenon is highly related to chronicity, but the concepts are not interchangeable.

At present, in societies with good access to healthcare, prevalence estimates of chronic depression provide the best estimate of TRD in the community. This is because adequacy of previous treatment and treatment resistance is not usually measured in community-based studies of depression and is difficult to assess retrospectively in clinical studies. This was the case when I attempted to identify TRD cases in the 2007 NSMHWB. Chronic depression has been reconceptualised in DSM-5 as Persistent Depressive Disorder and prevalence estimates of the new disorder may be more generalisable to TRD than prevalence estimates of DSM-IV Dysthymic

Disorder. This is because DSM-5 Persistent Depressive Disorder differs from DSM-IV Dysthymic Disorder by including all severity types. Previously, DSM-IV Dysthymic Disorder was considered to be a milder form of MDD as individuals were not allowed to meet criteria for an episode of depression during the first two years of the disturbance. However, this is no longer the case as DSM-5 Persistent Depressive Disorder encompasses all depression severities including milder DSM-IV Dysthymic Disorder and MDD with chronic specification. Thus, prevalence estimates of DSM-5 Persistent Depressive Disorder rather than DSM-IV Dysthymic Disorder are likely to be a more accurate reflection of the prevalence of TRD in societies which have relatively good access to healthcare

As Persistent Depressive Disorder is a recent addition to the DSM-5, no epidemiological data have been reported estimating its prevalence in community or clinical practice. The 2007 NSMHWB provided the opportunity to estimate the prevalence of DSM-5 Persistent Depressive Disorder. I estimated the lifetime prevalence of DSM-5 Persistent Depressive Disorder to be 4.6% (95% CI: 3.9–5.3%) in Australian community-residing individuals (Chapter Four). To date, this is the first published study to provide a prevalence estimate of the disorder. It is not yet clear what impact this disorder will have on the conceptualisation of TRD and whether the diagnosis will supersede the term TRD as the overarching label or catchall category of difficult-to-treat depression. One barrier to Persistent Depressive Disorder becoming a catchall category of difficult-to-treat depression is the extent to which clinicians will accept the overlap between Persistent Depressive Disorder and TRD. In addition, it is not clear whether clinicians will accept Dysthymia reconceptualised alongside chronic depression of all severities (i.e. including chronic MDD).

8.2.2 Definitions of TRD. As noted in the introductory chapter of the thesis, the concept of TRD is highly heterogeneous with no consensus on how to define it or identify it for research purposes or in clinical practice. An earlier systematic review of the conceptualisation of TRD identified that the failure of two antidepressants is the most commonly employed definition in RCTs of treatments for resistant depression (Berlim & Turecki, 2007b). I replicated the Berlim and Turecki (2007b) study using an additional 100 RCTs confirming the failure of two antidepressants as the most commonly used definition of TRD (Chapter Two). However, this definition must now be considered to be indicative of non-response rather than TRD as findings from the STAR*D study show that some MDD patients continue to respond to treatment even after the failure of two antidepressants.

Only 34.7% of RCTs (N = 51) reviewed in Chapter Two reported a mean number of prior antidepressant trials. The remaining 65.3% (N = 96) of RCTs reviewed did not report a mean number of prior antidepressant trials (see Chapter Two). From the 34.7% of RCTs which did report prior antidepressant trials the mean number of antidepressant trials received by participants prior to

entering the RCT was 5.3 (see Chapter Two). This mean is only slightly higher than the mean number of failed antidepressant trials found in my depressed inpatient sample (Mean = 5.03) (Chapter Six and Seven). This further indicates that the failure of two antidepressants is an inadequate definition of TRD because it is insufficiently strict. However, use of this definition of TRD is understandable in RCTs as a less constrained conceptualisation of TRD would increase the potential sample pool. This is an inherent flaw of many RCTs for depression as they do not reflect "real-world" patients presenting for treatment with major heterogeneity in clinical presentations and treatment response. Heterogeneity and variability in a sample of TRD patients is inevitable given the high level of co-morbidity and individual clinician bias when selecting treatment. Staging models of TRD provide more opportunity for variability by allowing patients to be rated with varying levels of TRD based on trialled treatments, symptom severity and illness duration. However, when I systematically reviewed RCTs in Chapter Two, the five staging models of TRD were rarely used to stage participants with TRD in RCTs of treatments for resistant depression. The use of staging models in research and clinical practice is impeded by the lack of validation studies. In particular, the models had not previously been cross-validated in the one study and against the usual definition of the failure of two antidepressants. Accordingly, I set out to assess the validity of the five available staging models of TRD and to investigate whether staging TRD on a continuum was superior to staging TRD dichotomously based on antidepressant failures (Chapter Six).

8.2.2.1 Validation of the available staging models of TRD. A sample of 70 depressed inpatients with TRD on all five staging models was used to empirically validate the five staging models of TRD (Chapter Six). The five models were highly correlated with one another, suggesting good concurrent validity. The depressed inpatient sample I recruited had trialled on average 5 antidepressants (SD = 3.0; median = 4; range = 1-13) with approximately 75% of participants failing three or more antidepressants (N = 54). Two regression models were used to ascertain whether there was any added benefit of rating TRD on a continuum rather than dichotomously, as the failure of three or more antidepressants. Rating TRD on a continuum provided more meaningful findings and was superior at explaining the variability in TRD in comparison to defining TRD dichotomously (see *5.4.8 Exploring predictors of TRD*). In research and clinical settings staging models can provide a measure of variability, track the progression of TRD over time and reduce heterogeneity in research by standardising related concepts such as treatment adequacy and trial failure.

Multidimensional staging models (i.e. the Maudsley Staging Method) incorporate additional measures of TRD such as symptom severity and illness duration. It is possible that these clinical features are not markers of TRD and add little to the overall utility and sensitivity of the model. Recently, Perlis (2013) attempted a clinical risk model for predicting the non-remission status of

STAR*D participants after one or two antidepressant trials. In total, 15 sociodemographic and clinical variables comprised the exploratory risk model including gender, education, marital status, race, symptom severity, presence of insomnia, presence of fatigue, presence of post-traumatic stress disorder (PTSD), episode recurrence, witnessing trauma, experiencing trauma, positive psychosis screen and impact of family and friends on illness course (Perlis, 2013). The risk model was only marginally successful in correctly identifying TRD cases (sensitivity = 26%) and was more successful in identifying patients without TRD (specificity = 91%) (Trivedi, 2013; Perlis, 2013). This further suggests that socio-demographic and clinical variables do not add to the classification power of current models and that additional unmeasured variables, most probably moderators or mediators, are involved in treatment response (Trivedi, 2013). Identifying endophenotypes (i.e. biological factors and/or genetic markers) that distinguish between varying levels of TRD may improve the classification of cases and add to the general predictive validity of staging models. Although speculative, endophenoytpes of interest may be discovered among changes in the neuroendocrine system, neurotransmitters, neurotrophic factors, and alterations in structure and function of the brain detectable using neuroimaging (see Chapter Six; Nasrallah, 2013).

8.3 Correlates of chronic and treatment-resistant depression.

Similarities and differences between individuals who respond to treatment and those who do not can provide insight into the aetiology of TRD. Additionally, factors that contribute to the maintenance of a chronic illness course might also be informative in regards to treatment response and resistance. The correlates of chronic depression and TRD were assessed in the thesis using data from the 2007 NSWHWB and clinical data on depressed inpatients.

When I modelled the DSM-5 diagnosis of Persistent Depressive Disorder using data from the 2007 NSMHWB and compared this chronic form of depression to non-chronic depression a high prevalence of co-morbid psychiatric disorders was found in the chronic depression group (Chapter Four). Because a large majority of the inpatient sample had a chronic illness duration it was not possible to replicate the 2007 NSMHWB finding that chronic depression is associated with a higher prevalence of co-morbid psychiatric diagnoses. However, considering at least two-thirds of the inpatient sample had a lifetime co-morbid DSM-IV psychiatric disorder it is likely that psychiatric co-morbidity is associated with treatment resistance (Chapter Six). Co-morbidity (both medical and psychiatric) is a known contributing factor to TRD (Souery et al., 2007) and is likely to be a strong contributor to the inpatient status of the sample. The high prevalence of psychiatric co-morbidity in the sample likely explains the non-significant association between higher levels of TRD and psychiatric co-morbidity in an OLS regression model (see Table 6.7). Thus, psychiatric

co-morbidity may be a correlate of chronic and treatment-resistant depression but it was not a risk factor for higher levels of TRD in the inpatient sample.

Both chronic depression (Chapter Four) and higher levels of TRD (Chapter Six) were associated with an earlier age of onset and an older current age. This may seem unsurprising as individuals with a longer illness duration (current age minus age of onset) would have a longer time to manifest a chronic and refractory illness. However, when this interaction was added to an OLS regression model it was found to be non-significant (Chapter Six). The notion that a chronic illness duration is not a necessary requirement for treatment resistance is supported by STAR*D findings which report it is possible to trial and fail four treatments within a 12-month period (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Therefore, in line with previous findings (Klein, 2010) an earlier age of onset may be a risk factor for chronic and treatment-resistant depression as an earlier age of onset may indicate a vulnerability to depression. An older current age may have a bidirectional relationship with chronic and treatment-resistant depression. This relationship may be mediated by age-related conditions such as cerebrovascular disease, which has been linked with a more chronic, and treatment resistant depressive illness (Rao, 2000). Additionally, poor cognitive functioning which was linked to higher levels of TRD in the inpatient sample could be considered a consequence of the chronic nature of TRD (Chapter Six). Alternatively, it could be a state effect (i.e. pseudodementia) or linked to dysfunctional neuroanatomic structures and circuits identified in introduction of Chapter Six.

A further consequence of chronic and treatment-resistant depression may be an increased risk of suicide. In the inpatient sample, higher levels of TRD, as rated by the composite TRD index, were associated with a higher prevalence of reported suicide attempts (Chapter Six). This finding may only be generalisable to inpatients, as treatment resistance, together with a suicide attempt may result in a higher likelihood of hospital admission. In support of this notion the chronic depression community-based sample in the 2007 NSMHWB (Australian Bureau of Statistics, 2007) had a lower rate of suicide attempts (20.6%) than the TRD inpatient sample (58.6%). Furthermore, the community-residing individuals with chronic depression identified in the 2007 NSMHWB who were treated in tertiary care settings had a higher rate of suicide attempts (51.2%) compared to chronically depressed individuals treated in primary care (13.8%) or those who have never been treated (6.1%) (Chapter Four). An increased risk of suicide in individuals with TRD and chronicity may involve feelings of helplessness and hopelessness after failing many treatments with little reprieve. Additionally, other factors associated with TRD could contribute to the high prevalence of suicide attempts including psychiatric co-morbidity, personality factors, medical co-morbidity, level of social support and psychosocial functioning.

As a whole, this thesis emphasised the shared correlates between chronic and treatment-resistant depression. This is despite methodological differences between chapters (i.e. treatment settings and study design). Shared correlates are an indication of the interrelatedness between chronic and treatment-resistant depression and provide evidence for their conceptual overlap.

8.3.1 Personality structures in TRD. Identification of a unique personality profile or maladaptive personality functioning in TRD could help to assist in identifying TRD patients in clinical practice, provide insight into the onset and maintenance of TRD, and assist clinicians in tailoring psychological treatments. As highlighted earlier in this chapter (Chapter Eight pp 195), very few predictors and risk factors for treatment resistance have been identified and scientific focus has now turned to potential mediators and/or moderators of TRD. Personality factors may moderate or mediate the relationship between particular aetiological factors and TRD. The presence of a particular personality trait together with one or more aetiological factors may increase the risk or vulnerability to developing TRD.

I examined the personality structure of depressed inpatients who were rated with TRD on the available staging models (Chapter Seven). The depressed inpatients' NEO-FFI personality profile was compared to informant ratings of the inpatients' personality and externally sourced comparative samples (depression in remission and never depressed controls). High scores on personality domains have previously been associated with maladaptive personality functioning and personality disorders (Samuel & Widiger, 2008; Piedmont, Sherman, & Sherman, 2012). Aberrations in personality ratings can be a reflection of current depressed state or a response bias. Informant data was used to determine the validity of patients NEO-FFI ratings. No significant differences in the means of the patients' and informants' ratings of personality were found. In addition, only modest correlations between the patients' ratings of personality and their current psychological distress were found. The patients' ratings of personality were deemed valid and not dependent on their mood state. As no differences between the patients' and informants' ratings were found a response bias was considered unlikely.

The depressed inpatients as a whole had a significantly different personality profile from the never depressed and depression in remission comparative samples. A pattern of high neuroticism, low extraversion, high openness to experience and low agreeableness and low conscientiousness characterised the depressed inpatients. The pattern of high neuroticism, low extraversion, low agreeableness and low conscientiousness has been associated with psychopathology in earlier studies (Trull & Sher, 1994). The finding suggests that the depressed inpatients, who were mainly chronic and had moderate to high levels of treatment resistance, have a personality profile which is reflective of psychopathology and differs significantly from the normal population.

The presence of high neuroticism and low extraversion in the inpatient sample was expected as depression has repeatedly been associated with high neuroticism and low extraversion (Akiskal, Hirschfeld, & Yerevanian, 1983; Fanous, Neale, Aggen, & Kendler, 2007; Katon, et al., 2002; Kotov, Gamez, Schmidt, & Watson, 2010; Mulder, 2002; Rosellini & Brown, 2011). In line with previous findings which suggest neuroticism is associated with worse treatment outcomes (Mulder, 2002) and a reduced likelihood of remission (Katon, et al., 2002), it could be inferred that a pervasively high level of neuroticism contributes to the onset and maintenance of depression over time. Alternatively, extremely high levels of neuroticism may be a 'scar effect' resulting from maintaining a high level of negative emotionality over a significant period of time as expected during a chronic and treatment resistant depressive illness. To determine whether maladaptive personality functioning is indeed a 'scar effect' would require the use of longitudinal research methods assessing personality functioning prior to the onset and over the course of the depression illness.

The personality domain of extraversion emerged as a potentially useful predictor of current psychological distress and suicide attempts in the inpatient sample. The high rate of suicide attempts found in the 2007 NSMHWB community-residing chronic depression sample (20.6%; Chapter Four) and the inpatient sample (58.6%; Chapter Six) highlights the high risk of suicide in these populations. Given that extraversion is associated with resilience, positive emotions and social support (Campbell-Sills, Cohan & Stein, 2006) it is understandable higher levels of extraversion would buffer against psychological distress and in turn decrease the risk of suicide attempts. Variations in the level of extraversion rather than neuroticism in depressed patients may be a more useful risk factor for suicidal attempts and could be a potential target for psychotherapy. This notion is confirmed by assessing the variability of the inpatient scores on extraversion and neuroticism using a measure of variability called the coefficient of variation (CV; see pp 151). Greater variability on extraversion (CV = 21.9%) compared to neuroticism (CV = 15.2%) was found in the inpatient sample. Therefore, given that neuroticism is universally high in depression with very little variation, extraversion may be a more clinically significant personality structure for psychotherapy and risk assessment.

Personality factors did not explain any additional variability in the TRD index above what was explained by sociodemographic and clinical variables (Chapter Seven, pp 180). As a whole, the sample was chronically depressed and had moderate to high levels of TRD. Therefore the failure to predict higher levels of TRD does not rule out the importance of personality factors in understanding and treating chronic and treatment-resistant depression. A personality profile of high neuroticism and openness domains together with low extraversion, agreeableness and conscientiousness was found in the sample suggesting these aberrations in personality structure may

predict a more chronic illness course and poorer response to treatment in individuals with depression.

8.4 Validity and Usefulness of the term TRD

Despite concerns about its measurement, there is no denying that the phenomenon of non-response to treatment in individuals with depression exists. Evidence from large multi-centre trials, such as the STAR*D, and meta-analyses of clinical trial data highlight the lower than expected efficacy rates of our current treatments for depression. To acknowledge the existence of non-response to treatment, the phenomenon must be named and conceptualised. As we know, it is most commonly conceptualised as TRD. However, it is questionable whether current operational definitions of TRD are valid and useful for both researchers and clinicians.

8.4.1 Calling a spade a spade. In order to study any phenomenon or illness state it must be labelled and defined in a way that is operational. Since the 1970s, the non-response to treatment for individuals with depression has been acknowledged and labelled first as treatment refractory depression and later as TRD. Despite naming the phenomenon and acknowledging its existence over 40 years ago, the field of psychiatry has not settled on how to define it and more importantly, how to operationalize it. This is not for want of trying. There have been many attempts to standardise the concept of TRD using either a dichotomous definition of the failure of two antidepressants or by staging TRD on a continuum of resistance. However, no single model has been adopted for widespread use by researchers and clinicians. Additionally, non-pharmaceutical treatments for depression (e.g. psychotherapy, ECT, TMS, VNS) are not included in many models of TRD. Thus, the models fail to fully encompass the complete phenomenon of non-response to treatment.

There has been a rise in the number of RCTs conducted in patients with TRD in recent years (see Chapter Two). Despite this growing interest in developing new treatment strategies for TRD patients, the findings are difficult to interpret and replicate due to major variations in the operationalisation of TRD from study to study. Non-clinical trial data on TRD are less common and there are a limited number of naturalistic cohort or case-control studies, which investigate the phenomenon. Additionally, there has been no clear consensus on why or how some patients become treatment-resistant. Even though risk factors for TRD and theories of resistance have been put forward in medical scientific literature we are no closer to understanding the aetiology of TRD and no closer to prospectively identifying which patients are likely to be poor responders to treatment. Clinical prediction models, such as Perlis' model (2013; see pp 174), have not been successful at identifying TRD in clinical populations, suggesting that other, unmeasured, variables (e.g. endophenotypes) are likely to be involved in treatment resistance.

Why is the phenomenon of non-response to treatment so difficult to conceptualise and operationalize? One partial explanation could be that TRD is not diagnosable as a distinct disorder in the DSM-5 or ICD-10 and therefore open to continual interpretation and conceptualisation. Alternatively, the failure to conceptualise and operationalise TRD in a clinically meaningful way could be linked to how we conceptualise depression more generally. The DSM-5 proposes that depression occurs in discrete episodes which when treated effectively, results in a return to premorbid functioning and wellness. However, this is not the case for a large proportion of patients. Depression is likely to recur and in almost one-third of patients it follows a chronic illness trajectory (Murphy & Byrne, 2012). In recent times, there has been a shift in psychiatry, acknowledging that depression is not as treatable and episodic as once thought. Furthermore, the current armamentarium for treating depression appears to be no more effective than it was 50 years ago despite ongoing research efforts.

It could be argued that we have outgrown our current diagnostic classification for depression because it no longer adequately reflects what we know about the disorder and how it is treated. The only major revision to the conceptualisation of depression in the past 35 years has been the removal of the bereavement exclusion from the DSM-5. This could have a considerable impact on the conceptualisation of depression by failing to delineate normal sadness from clinical depression or sadness without cause. However, this is yet to be seen. Even prior to the removal of the bereavement exclusion, there were growing concerns that heterogeneous presentations of depression were being fitted into a homogenous diagnostic classification system largely ignoring aetiology and symptom clusters representing depression subtypes e.g. melancholia and atypical depression. As a consequence, TRD has developed its own heterogeneity with resistance to treatment occurring for multiple reasons, at different points during the illness course and to specific treatments only. An additional caveat of depression research is the constant struggle between calling for more standard treatment selection to systematically assess treatment efficacy and the recognition that different symptom clusters (or depression subtypes) require different treatments. The conceptualisation of the disorder, as the endorsement of one or two core symptoms (depressed mood or anhedonia) alongside four or more other depression symptoms is arbitrary and creates major heterogeneity in clinical presentations. Without the reconceptualization of depression, both treatment approaches cannot occur simultaneously. Staging depression in a similar way to medical diseases such as cancer or infectious diseases may provide the opportunity to systematically guide treatment selection based on clinical presentation and the progression of the disorder.

8.4.2 An alternative to the term TRD: illness staging for depression. Illness and disease staging is common practice in medical fields, especially in oncology and cardiology (Ferensztajn, Remlinger-Molenda & Rybakowski, 2014). Illness staging allows for differentiation between early

and mild forms of the illness/disease and more severe and chronic forms (McGorry et al., 2010). Furthermore, it allows for a patient to be placed on a continuum of illness progression and treated accordingly (McGorry et al., 2010). Psychiatric disorders are considered to be perfect candidates for illness staging because many severe mental disorders have identifiable risk factors, a prodromal stage, illness progression with marked deterioration or worsening of symptoms and functional decline (Lin, Reniers & Wood, 2013). Over 20 years ago Fava and Kellner (1993) proposed staging psychiatric disorders in a similar way to other medical fields. Schizophrenia and Bipolar Affective Disorder have received the most attention, with several illness staging models developed (Ferensztajin, Remlinger-Molenda & Rybakowski, 2014). The concept of TRD has also been continually staged over the years. The staging of depression more generally which incorporates sub-threshold depression syndromes, depressive reactions and chronic depression has received less interest compared to TRD staging.

Fava and Tossani (2007) put forward the first staging model for unipolar depression. They characterise Stage 1 as the prodromal phase which features the onset of subdepressive symptoms, most notably anxiety, irritable mood, anhedonia and sleep disturbance. Stage 2 is characterised by the first onset of a depression episode. Stage 3 is the residual phase of the illness with full remission or dysthymia (no remission). Stage 4 is indicative of recurrent depression or double depression, and stage 5 is chronic depression lasting at least two years with no wellness periods (Fava & Tossani, 2007). McGorry et al., (2010) went one step further and defined each illness stage, as well as, potential interventions, relevant patient populations and indicative endophenotypic markers for psychotic and severe mood disorders. It is the most comprehensive model to date. However, McGorry et al., (2010) does not incorporate neurobiological findings which characterise the progression of psychiatric disorders from the prodromal stage to Stage 4 and 5(Nasrallah, 2013). This is has become increasingly important as evidence suggests, recurrent and chronic depression states result in inflammation, oxidative stress and loss of neurotrophic factors leading to potentially irreversible neuronal circuit damage and functional and structural brain atrophy (Nasrallah, 2013). This inevitability will be the focus of future research and refinement of staging models going forward.

In both models, the final stage is a severe and persistent illness. Moller et al. (2013) proposed employing one of the following terms, ‘malignant’, ‘pernicious’ or ‘virulent’ to characterise the end stage of depression and TRD. Relabelling TRD as malignant or virulent depression triggers connotations related to the seriousness of the disorder, high mortality rates and its untreatable nature. Associating TRD with medical staging connotations could lead to more urgent clincial intervention and spur further research efforts.

8.5 Strengths and Contributions of Thesis

The major strength of this thesis is the use of multiple research methodologies ranging from a systematic review to analyses of primary and secondary data. This approach enabled the phenomena of chronic and treatment-resistant depression to be evaluated at both the epidemiological and tertiary care level. The major pitfalls surrounding how treatment-resistant depression is conceptualised are highlighted (see Chapter Two). To my knowledge, this thesis includes the largest systematic review (N = 147 articles) exploring current concepts and staging models of TRD used in RCTs. This systematic review reports the inconsistencies in definitions and the limited use of available staging models to identify and rate TRD. Following on from this, the five available staging models are compared using a sample of depressed inpatients (see Chapter Six). To my knowledge, this is the first body of research to compare the five staging models of TRD using the same sample of depressed patients. All models were highly related and a composite index of TRD was created to assess the usefulness of rating TRD on a continuum rather than dichotomously. Considering not one of the staging models of TRD has been adopted for widespread use it was important to assess whether staging models provide any usefulness above and beyond what is provided by simpler definitions as the failure of three or more antidepressants. As expected, rating TRD on a continuum provided more meaningful results and understanding of the phenomenon.

An additional strength of this thesis was its investigation of both chronic and treatment-resistant depression in the Australian context. A large national survey (2007 NSMHWB) was used to estimate the prevalence of chronic and treatment-resistant depression in the Australian community and a sample of depressed inpatients were recruited from an Australian private hospital. A published paper on DSM-5 Persistent Depressive Disorder which utilised data from the 2007 NSMHWB was incorporated into the thesis. To date, these are the only Australian epidemiological data published on the new diagnosis and provide the first estimate of the prevalence of this disorder in the Australian community.

A notable feature of the thesis is the analysis of the health services utilised by individuals with chronic depression and the differences in services accessed by chronically depressed individuals (e.g. untreated, primary care or tertiary) (see Chapter Four). This analysis provided context for the following two empirical chapters which investigated the degree of chronic and treatment resistant depression in tertiary care (see Chapter Six and Seven). The majority of previous studies on chronic and treatment-resistant depression report findings on depressed outpatients. Therefore this thesis is unique by providing an insight into the prevalence of chronic and treatment-resistant depression in tertiary care settings. Subsequently this allowed detailed discussion on the clinical implications of identifying and treating TRD patients in clinical practice and tertiary care.

Additionally, the thesis emphasised the burden of chronic and treatment-resistant depression on tertiary care settings and the lack of standardised tools to identify and treat patients with TRD.

8.6 Limitations of Thesis

Despite the strengths listed above there were several shortcomings of the thesis that need to be discussed. The ongoing circularity and overlap between the concepts of chronic and treatment-resistant depression could not be avoided. This is most likely due to the ever-changing and evolving conceptualisations of both chronic and treatment-resistant depression and also the unavoidable similarities between both concepts. In relation to this, the inpatient sample reported in this thesis had some obvious limitations. Firstly, the depressed inpatients were recruited as a sample of convenience. The sample of convenience may explain the modest variability in particular illness characteristics such as chronicity and symptom severity. Minimal variability in the sample may also be explained by the inpatient status of patients and their current depressed state leading to admission to hospital. It is also likely that the high levels of psychiatric comorbidity exhibited by the inpatient sample might have contributed to the likelihood of hospital admission. Due to the specific nature of the treatment setting, the findings are not readily generalisable to outpatients with TRD or to individuals who self-manage their depression.

Only inpatients well enough to participate were recruited and a sample of treatment responsive or healthy controls were not included. To assess maladaptive personality functioning, the depressed inpatients were compared to externally sourced controls in an attempt to combat this limitation. However, externally sourced comparative samples are not a perfect substitute for primary data. Furthermore, the findings were heavily reliant on patient recall and chart auditing for historical treatment and illness course data. Medical records and patient recall do not provide a perfect record of historical information for every patient. Furthermore, patients' current depressed state at time of assessment may have affected their ability to be reliable historians. This is a definite drawback of cross-sectional research designs which could be appropriately addressed by a longitudinal research study design.

Despite reviewing the biological correlates of TRD and acknowledging the relevance of biological correlates in antidepressant non-response it was beyond the scope of the thesis to investigate these. This might have limited the ability to draw definitive conclusions about the pathogenesis of TRD and could be addressed in future research.

8.7 Directions for Future Research

Longitudinal research studies are required to assess the course and treatment response of depression over time. These need to incorporate standardised treatment selection tools in order to

limit the effects of individual clinician bias and to study the phenomenon in a consistent manner. As with the STAR*D study, a longitudinal study with multiple standardised stages of treatment with randomised treatment selection would provide much needed information on the onset and course of TRD.

As longitudinal studies are not always feasible, cross-sectional studies investigating TRD should include a contemporaneous control group of depressed patients who are treatment responsive or previously depressed individuals who are now euthymic. Findings from TRD studies which do not include a control group are difficult to generalise to TRD exclusively, as the findings cannot be distinguished from depression more generally. This is especially important when investigating the biological markers of TRD. The inclusion of control groups would enable the identification of potential mediators and moderators of treatment resistance.

Further validation studies of the staging models are required in order to test the clinical utility of the models in everyday practice. The future elucidation of biomarkers and features of TRD may result in more complex and effective models.

8.8 Overall Conclusion

Chronic and treatment-resistant depression are highly prevalent and disabling, and associated with many poor long-term outcomes. This thesis has highlighted the conceptual overlap between chronic and treatment-resistant depression. The overlap has arguably become more prominent with the addition of Persistent Depressive Disorder in the DSM-5. Current heterogeneity and inconsistency in the conceptualisation of TRD was emphasised in the early chapters of the thesis. The final empirical chapters investigated TRD in more depth by recruiting depressed inpatients and rating the inpatients with TRD on the available staging models. Many of the correlates of TRD identified in the thesis are most likely consequences of the chronic and unremitting nature of resistant depression. Furthermore, it is likely that these factors have a bidirectional relationship with TRD especially age, poor psychosocial functioning and poor occupational functioning. Resistance to treatment over a long-period of time is likely to contribute to the poor functioning found in this population, as well as, the disease burden posed by depression more generally. Moreover, patients with higher levels of TRD are at a greater risk of suicide likely due to hopelessness from trialling multiple treatments with very little success.

This thesis contributes to the body of literature on TRD and highlights the clinical and individual burden posed by resistant depression in inpatient settings. Throughout this thesis the previous ambiguous and inconsistent study of the phenomenon was emphasised. The clinical utility of various definitions and staging models of TRD were investigated in order to contribute to the current conceptualisation of TRD. In addition the clinical implications of treating patients with

chronic and treatment-resistant depression were explored. Longitudinal research methods together with the consideration of staging depression in a similar way to other medical illness is needed in order to further our knowledge of chronic and treatment-resistant depression and determine why some individuals do not respond to treatment and reach sustained remission.

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Appendix 1. Five staging models of TRD

1. Antidepressant Treatment History Form (ATHF)

Treatment trials	Score
1. Tricylics/Heterocyclics	
A. Amitriptyline, imipramine, desipramine, trimipramine, clomipramine, maprotiline, doxepin, nomifensine	
Any drug < 4 weeks or any drug < 100mg/day	1
4 weeks or more and 100-199 mg/day	2
4 weeks or more and 200-299 mg/day	3
4 weeks or more and 300mg/day or greater	4
B. Nortriptyline	
< 4 weeks OR 4 weeks or more dosage < 50mg/day	1
4 weeks or more and dosage 50-75 mg/day	2
4 weeks or more and dosage 76-100 mg/day	3
4 weeks or more and dosage > 100	4
C. Protriptyline	
< 4 weeks OR 4 weeks or more and dosage < 30 mg/day	1
4 weeks or more and dosage 31-40mg/day	2
4 weeks or more and dosage 41-60mg/day	3
4 weeks or more and dosage > 60mg/day	4
II. Selective serotonin reuptake inhibitors	
A. Fluoxetine	
< 4 weeks or more OR 4 weeks or more and dosage 1-9 mg/day	1
4 weeks or more and dosage 10-19mg/day	2
4 weeks or more and dosage 20-39mg/day	3
4 weeks or more and dosage ≥ 40mg/day	4
B. Fluvoxamine	
< 4 weeks OR dosage < 100mg/day	1
4 weeks or more and dosage 100-199mg/day	2
4 weeks or more and dosage 200-299mg/day	3
4 weeks or more and dosage 300mg/day or greater	4
C1. Paroxetine	
< 4 weeks OR 4 weeks or more and dosage < 1-9 mg/day	1
4 weeks or more and dosage 10-19mg/day	2
4 weeks or more and dosage 20-29mg/day	3
4 weeks or more and dosage ≥ 30mg/day	4
C2. Paroxetine CR	
< 4 weeks OR 4 weeks or more and dosage < 12.5mg/day	1
4 weeks or more and dosage 12.5mg/day	2
4 weeks or more and dosage 25-50mg/day	3
4 weeks or more and dosage ≥ 62.5mg/day	4
D. Sertraline	
< 4 weeks OR 4 weeks or more and dosage <50mg/day	1
4 weeks or more and dosage 50-59mg/day	2
4 weeks or more and dosage 100-199mg/day	3
4 weeks or more and dosage ≥ 200mg/day	4
E. Citalopram	
< 4 weeks OR 4 weeks or more and dosage 1-9mg/day	1
4 weeks or more and dosage 10-19mg/day	2
4 weeks or more and dosage 20-39mg/day	3
4 weeks or more and dosage ≥ 40mg/day	4

F. Escitalopram	
< 4 weeks OR 4 weeks or more and dosage 1- 4mg/day	1
4 weeks or more and dosage 5-9mg/day	2
4 weeks or more and dosage 10-19mg/day	3
4 weeks or more and dosage ≥ 20mg/day	4
III. Selective serotonin and norepinephrine reuptake inhibitors	
A. Duloxetine	
< 4 weeks OR 4 weeks or more and dosage < 30mg/day	1
4 weeks or more and dosage 30-39mg/day	2
4 weeks or more and dosage 40-59mg/day	3
4 weeks or more and dosage ≥ 60mg/day	4
B. Venlafaxine	
< 4 weeks OR 4 weeks or more and dosage < 75mg/day	1
4 weeks or more and dosage 75-224mg/day	2
4 weeks or more and dosage 225-374mg/day	3
4 weeks or more and dosage ≥ 375mg/day	4
IV. Monoamine Oxidase Inhibitors	
A. Phenelzine	
< 4 weeks OR 4 weeks or more and dosage <30mg/day	1
4 weeks or more and dosage 31-60mg/day	2
4 weeks or more and dosage 61-90mg/day	3
4 weeks or more and dosage ≥ 91mg/day	4
B. Moclobemide	
< 4 weeks OR 4 weeks or more and dosage <150mg/day	1
4 weeks or more and dosage 150-299mg/day	2
4 weeks or more and dosage 300-599mg/day	3
4 weeks or more and dosage ≥ 600mg/day	4
C. Selegiline	
< 4 weeks OR 4 weeks or more and dosage <20mg/day	1
4 weeks or more and dosage 21-40mg/day	2
4 weeks or more and dosage 41-59mg/day	3
4 weeks or more and dosage ≥ 60mg/day	4
D. Tranylcypromine	
< 4 weeks OR 4 weeks or more and dosage < 20mg/day	1
4 weeks or more and dosage 21-40mg/day	2
4 weeks or more and dosage 41-60mg/day	3
4 weeks or more and dosage ≥ 61mg/day	4
V. Other antidepressants	
A. Bupropion	
< 4 weeks OR 4 weeks or more and dosage <150mg/day	1
4 weeks or more and dosage 150-299mg/day	2
4 weeks or more and dosage 300-449mg/day	3
4 weeks or more and dosage ≥ 450mg/day	4
B. Mirtazapine	
< 4 weeks OR 4 weeks or more and dosage <15mg/day	1
4 weeks or more and dosage 15-29mg/day	2
4 weeks or more and dosage 30-44mg/day	3
4 weeks or more and dosage ≥ 45mg/day	4
C. Nefazodone	
< 4 weeks or 4 weeks or more and dosage <150mg/day	1
4 weeks or more and dosage 150-299mg/day	2
4 weeks or more and dosage 300-599mg/day	3

4 weeks or more and dosage ≥ 600mg/day	4
D. Trazodone	
< 4 weeks or 4 weeks or more and dosage <150mg/day	1
4 weeks or more and dosage 150-299mg/day	2
4 weeks or more and dosage 300-599mg/day	3
4 weeks or more and dosage ≥ 600mg/day	4
E. Reboxetine	
< 4 weeks or 4 weeks or more and dosage < 200mg/day	1
4 weeks or more and dosage 150-299mg/day	2
4 weeks or more and dosage 300-599mg/day	3
4 weeks or more and dosage ≥ 600mg/day	4
VI. ECT	
A. Unilateral ECT	
1-3 ECT	1
4-6 ECT	2
7-9 ECT	3
10-12 ECT	4
13 or more ECT	5
B. Bilateral ECT	
1-3 Bilateral ECT	1
4-6 Bilateral ECT	2
7-9 Bilateral ECT	4
10 or more Bilateral ECT	5
VII. Non-pharmacological somatic therapies	
A. Vagnus Nerve Stimulation (VNS)	
< 6 months	1
6-11 months	2
12-24 months	3
> 24 months	4
B. Transcranial Magnetic Stimulation (TMS)	
< 10 sessions	1
10-14 sessions	2
15-19 sessions	3
≥ 20 sessions	4
VIII. Augmentation therapies	
A. Lithium alone	
< 4 weeks or 4 weeks or more and dosage <600mg/day	1
4 weeks or more and dosage 600-899mg/day	2
4 weeks or more and dosage ≥ 900mg/day	3
B. Lithium as an augmentation agent	
Antidepressant drugs I-IX scored 3 and lithium for at least 2 weeks or carbamazepine scored 3 and lithium for at least 2 weeks	1
Antidepressant drugs I-IX scored 4 and lithium for at least 2 weeks	2
C. Carbamazepine	
< 4 weeks or 4 weeks or more dosage < 400mg/day	1
4 weeks or more and dosage 400-999mg/day	2
4 weeks or more and dosage ≥ 1000mg/day	3
D. Lamotrigine	
< 4 weeks or 4 weeks or more dosage <150mg/day	1
4 weeks or more and dosage 150-299mg/day	2
4 weeks or more and dosage ≥ 300mg/day	3
E. Thyroid hormone	

< 4 weeks	1
> 4 weeks or more and dosage <25mcg/day	2
> 4 weeks or more and dosage 25-49mcg/day	3
> 4 weeks or more and dosage ≥ 50mcg/day	4
IX. Benzodiazepines	
A. Alprazolam	
Alprazolam < 4 weeks or 4 weeks or more and dosage < 6mg/day	1
4 weeks or more and dosage 6mg/day or greater	2
B. Other benzodiazapines	
Any dosage for any duration	1
X. Miscellaneous	
A. Stimulants	
Any dosage for any duration	1
B. Antipsychotics	
Any dosage for any duration	1
C. Clonidine, L-tryptophan, thyroid hormones, estrogen, fenfluramine	
Any dosage for any duration	0
D. Sedatives	
Any dosage for any duration	1
E. Phototherapy	
In any form	1
XI. Psychotherapy	
A. Cognitive behavioural therapy (CBT)	
< 4 visits	1
4-11 visits	2
12-15 visits	3
16 or more visits	4
B. Interpersonal therapy (IPT)	
< 4 visits	1
4-11 visits	2
12-15 visits	3
16 or more visits	4
C. Behavioural activation therapy	
< 4 visits	1
4-11 visits	2
12-15 visits	3
16 or more visits	4

Total score = the summation of each treatment trial (1 – no definitive maximum)

Adapted from Oquendo, et al., 2003; Sackeim, Prudic, Devanand, Decina, Kerr, & Malitz, 1990

2. Thase and Rush Model (TRM)

Stage	Definition	Score
I	Failure of at least 1 adequate trial of 1 major class of antidepressants	1
II	Failure of at least 2 adequate trials of at least 2 distinctly different classes of antidepressants	2
III	Stage II resistance plus failure of an adequate trial of a TCA	3
IV	Stage III resistance plus failure of an adequate trial of an MAOI	4
V	Stage IV resistance plus a course of bilateral ECT	5

Total score = 1 – 5

Adapted from Thase and Rush, 1997

3. European Staging Model (ESM)

Stage	Definition	Duration	Score
A. Non-responder	Non-response to 1 adequate trial of TCA, SSRI, MAOI, SNRI, ECT or other antidepressants	6 -8 weeks	1
B. TRD	Resistance to 2 or more adequate antidepressant trials of different classes	TRD1: 12-16 weeks	2
		TRD2: 18 – 24 weeks	3
		TRD3: 24 – 32 weeks	4
		TRD4: 30 – 40 weeks	5
		TRD5: 36 weeks – 1 year	6
C. CRD	Resistant to several antidepressant trials (at least 5 trials), including augmentation strategy	At least 12 months	7

Total score = 1 - 7

Adapted from Souery, et al., 1999

4. Massachusetts General Hospital Staging Model (MGHS)

Stage	Definition	Score
1	Non-response to each adequate (at least 6 weeks of an adequate dosage of an antidepressant) trial of a marketed antidepressant generates an overall score of resistance	1 point per trial
2	Optimisation of dose, optimisation of duration and augmentation or combination of each trial increase the overall score	0.5 point per trial per optimisation or augmentation strategy
3	Electroconvulsive therapy	3 points

Total score = the summation of each treatment trial (1 – no definitive maximum)

Adapted from Fava, 2003

5. Maudsley Staging Model (MSM)

Parameter	Specification	Score
Duration	Acute (≤12 months)	1
	Sub-acute (13 – 24 months)	2
	Chronic (>24 months)	3
Symptom severity	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures	Level 1: 1 – 2 medications	1
	Level 2: 3 – 4 medications	2
	Level 3: 5 – 6 medications	3
	Level 4: 7 –10 medications	4
	Level 5: > 10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
	Used	1

Total score = 3 – 15

Adapted from Fekadu et al., 2009

Appendix 2. Summary of information extracted from included RCTs

	Author/Year	Focus	N	Terminology	Definition	Symptom Cut-Offs	Dose of previous trial	Duration of previous trial	Compliance	Model	Diagnosis
1.	Aaronson et al., 2013	VNS	331	Treatment-resistant depression	≥ 4 AD from 2 different classes	MADRS ≥ 24	Adequate	Adequate	Not reported	No model reported	DSM-IV of chronic or recurrent MDD or Bipolar Disorder and current MDE
2.	Alexopoulos et al., 2008	Augmentation	489	Treatment-resistant depression	≥ 1 but no more than 3AD during the current episode	HAM-D (17) ≥20	Within ranges approved by the FDA	≥ 6 weeks	Not reported	No model	DSM-IV MDD
3.	Amsterdam et al., 2009	Augmentation	276	Treatment-resistant depression	Not reported	HAM-D (17) ≥18	Not reported	Not reported	Not reported	No model	DSM-IV of recurrent MDD with at least 1 prior depressive episode in the previous 3
4.	Anderson et al., 2007	TMS	29	Treatment-resistant depression	Not reported	Not reported	Not reported	Not reported	Not reported	No model	DSM-IV MDE
5.	Avery et al., 1999	TMS	6	Medication Resistant	≥ 2 AD in the current episode	SIGH-SAD ≥ 20	Not reported	Not reported	Not reported	No model	DSM-IV MDD
6.	Avery et al., 2006	TMS	68	Medication Resistant	≥ 2 AD in the current or any prior episode	HAM-D (17) ≥ 17	ATHF	ATHF	Not reported	Thase and Rush	DSM-IV MDD
7.	Barbee et al., 2011	Augmentation	183	Refractory	≥ 1 AD in current episode	HAM-D (17) ≥ 18	Minimum required dose	≥ 6 weeks	Not reported	Thase and Rush	DSM-IV MDD and ICD-10 Depression
8.	Barbosa, Berk & Vorster, 2003	Augmentation	23	Resistant	≥ 1 AD excluding Fluoxetine	HAM-D (17) ≥ 18	Adequate dose	6 weeks	Not reported	No model	DSM-IV MDE
9.	Bares et al., 2009	TMS	60	Treatment-resistant depression	≥ 1 AD in current episode	MADRS ≥ 20	ATHF	ATHF	Not reported	Thase and Rush	DSM-IV MDD
10.	Barker, Scott & Eccleston 1987	Combination	20	Treatment-resistant chronic depression	Depressed for at least 2 years and had failed to respond to recognised treatment regimes	Not reported	Not reported	Not reported	Not reported	No model	RDC Major Depressive Illness
11.	Baumann et al., 1996	Augmentation	69	Therapy resistant	1 AD (Citalopram)	HAM-D (21) ≥ 18	40mg/day to 60mg/day of Citalopram	4 weeks	Not reported	No model	DSM-III MDD

12.	Berman et al., 2000	TMS	20	Treatment-resistant depression	≥ 1 AD in current or previous episodes	HAM-D (25) no cut-off specified	Equivalent to 200mg/day of Imipramine, 20 mg/day Fluoxetine, 60mg/day Phenelzine, 225mg/day Venlafaxine or 30mg/day Mirtazapine	≥ 4 weeks	Not reported	No model	DSM-IV MDE
13.	Berner, Kryspin-Exner & Poeldinger, 1974	Multiple therapies	55	Therapy resistant	2 AD	Not reported	Not reported	Not reported	Not reported	No model	Not reported
14.	Birkenhager et al., 2004	Augmentation	138	Refractory	Failure to respond to adequate pre-treatment with AD	HAM-D (not specified) ≥ 17	Adequate plasma levels	≥ 4 weeks	Plasma levels monitored	No model	DSM-IV MDD
15.	Blumberger et al., 2012a	TMS	74	Treatment-resistant depression	Thase and Rush	HAM-D (17) ≥ 21	Adequate	≥ 6 weeks	Not reported	Thase and Rush	DSM-IV MDD
16.	Blumberger et al., 2012b	TMS	24	Treatment-resistant depression	Thase and Rush	HAM-D (17) ≥ 21	Adequate	≥ 6 weeks	Not reported	Thase and Rush	DSM-IV MDD
17.	Boutros et al., 2002	TMS	21	Treatment-resistant depression	≥ 2 AD	HAM-D (25) ≥ 20	Not reported	Not reported	Not reported	No model	DSM-IV MDD
18.	Bretlau et al., 2008	TMS	45	Medication resistant	≥ 1 AD in current episode	Not reported	Equivalent to 200mg/day of Imipramine for TCAs; 40mg/day Paraoxetine for SSRIs, 225mg/day of Venlafaxine; 60mg/day Mirtazapine	≥ 6 weeks	Excluded if non compliant	No model	DSM-IV MDD
19.	Carta et al., 2008	Physical Exercise	30	Resistant	≥ 1 AD	HAM-D (not spec) > 13 after at least 2mnths of pharmacological treatment	Adequate dose	Not reported	Not reported	No model	DSM-IV MDE
20.	Chaput, Magnan & Gendron, 2008	Augmentation	31	Refractory	≥ 2 AD of different classes	HAM-D (21) ≥ 20 and CGI-S ≥4	Be at or near the highest therapeutically recommended doses for 3 weeks of the trial	≥ 8 weeks	Capsule counts of returned medication	Thase and Rush	DSM-IV MDD
21.	Chen et al., 2013	TMS	21	Treatment-resistant depression	≥ 2 AD	HAM-D (17) ≥ 18	Not reported	6 weeks	Not reported	No model reported	DSM-IV MDD
22.	Corya et al., 2006	Combination	483	Treatment-resistant depression	≥ 2 AD	CGI-S ≥4	Therapeutic dose	≥ 6 weeks	Self-report	No model	DSM-IV MDD

23.	Cusin et al., 2013	Augmentation	60	Treatment Resistant MDD	≥ 1 SSRI or SNRI	MADRS ≥ 18	Adequate	≥ 6 weeks	Not reported	Not reported	DSM-IV MDD
24.	Davidson et al., 1978	ECT vs. combination	17	Refractory	Treated unsuccessfully with conventional psychotropic drugs	Not reported	Adequate dose	Not reported	Not reported	No model	Diagnostic criteria for use in Psychiatric Research (1972) unipolar depression or depr disorder
25.	DeBattista et al., 2011	rEEG-guided pharmacotherapy	114	Resistant	≥ 1 SSRIs in current episode or ≥ 2 AD of two classes in the current episode	MADRS > 26 and QIDS-SR16 ≥13	Not reported	Not reported	Excluded if non compliant	No model	DSM-IV MDD
26.	Doree et al., 2007	Augmentation	20	Treatment-resistant depression	≥ 1 AD	HAM-D (17) ≥ 20 and CGI-S ≥4	Maximum dose	≥ 4 weeks	Not reported	No model	DSM-IV MDD
27.	Drago,, Motta & Grossi, 1983	Monotherapy	40	Resistant	3 AD in the previous 6 months	HAM-D (17) ≥18	Not reported	Not reported	Not reported	No model	Depression according to Feighner criteria
28.	Dunner et al., 2007	Augmentation	64	Treatment-resistant depression	≥ 2 AD either an SSRI or SNRI	MADRS ≥ 20	Adequate dose	Adequate duration	Not reported	No model	DSM-IV MDD
29.	Fang et al., 2010	Monotherapy	114	Treatment-resistant depression	≥ 2 AD from different classes	HAM-D (17) ≥ 17	Adequate dose	≥ 3 months	Not reported	Thase and Rush	DSM-IV MDD
30.	Fang et al., 2011	Augmentation	225	Treatment-resistant depression	≥ 2 AD from different classes	HAM-D (17) ≥ 17	Not reported	Not reported	Not reported	Thase and Rush	DSM-IV MDD
31.	Fava et al., 1994	Augmentation	41	Resistant	1 AD (Fluoxetine)	HAM-D (17) ≥16	20mg/day Fluoxetine	8 weeks	Not reported	No model	DSM-III MDD
32.	Fava et al., 2012	Augmentation	225	Inadequate response	≥ 1 AD but no more than 3AD	HAM-D (17) ≥ 18	Adequate dose	≥ 8 weeks	Not reported	No model	DSM-IV MDE
33.	Fitzgerald et al., 2003	TMS	60	Treatment-resistant depression	≥ 2 AD	MADRS > 20	Not reported	≥ 6 weeks	Not reported	No model	DSM-IV MDD
34.	Fitzgerald et al., 2006	TMS	50	Treatment-resistant depression	≥ 2 AD	MADRS > 20	Standard effective dose	≥ 6 weeks	Not reported	Thase and Rush	DSM-IV MDD
35.	Fitzgerald et al., 2006	TMS	50	Treatment-resistant depression	≥ 2 AD	MADRS > 20	Standard effective dose	≥ 6 weeks	Not reported	Thase and Rush	DSM-IV MDD
36.	Fitzgerald et al., 2007	TMS	26	Treatment-resistant depression	≥ 2 AD in current episode	MADRS > 20	Not reported	≥ 6 weeks	Not reported	No model	DSM-IV MDD

37.	Fitzgerald, 2008	TMS	50	Treatment-resistant depression	≥ 2 AD	MADRS > 20	Stable dose	6 weeks	Not reported	Thase and Rush	DSM-IV MDD
38.	Fitzgerald et al., 2008	TMS	60	Treatment-resistant depression	≥ 2 AD in current episode	MADRS > 20	Not reported	≥ 6 weeks	Not reported	Thase and Rush	DSM-IV MDD or DSM-IV Bipolar I or II (depressed phase)
39.	Fitzgerald et al., 2009a	TMS	27	Treatment-resistant depression	≥ 2 AD in current episode	MADRS > 20	Not reported	≥ 6 weeks	Not reported	No model	DSM-IV MDD
40.	Fitzgerald et al., 2009b	TMS	51	Treatment-resistant depression	≥ 2 AD in current episode	MADRS > 20	Not reported	≥ 6 weeks	Not reported	Thase and Rush	DSM-IV MDD
41.	Fitzgerald et al., 2012	TMS	67	Treatment-resistant depression	≥ 2 AD in current episode	HAM-D (17) > 15	Not reported	≥ 6 weeks	Not reported	Thase and Rush	Moderate/severe depression as per the MINI
42.	Fitzgerald et al., 2013	TMS	179	Treatment-resistant depression	Thase and Rush stage II	HAM-D (17) ≥ 13	Adequate	≥ 6 weeks	Not reported	Thase and Rush	DSM-IV MDD or DSM-IV Bipolar I or II (depressed phase)
43.	Folkerts et al., 1997	ECT	39	Treatment-resistant depression	≥ 2 AD (including 1 TCA)	HAM-D (21) ≥ 22	Equivalent to 100mg Imipramine	≥ 8 weeks	Not reported	No model	ICD-10 Depression
44.	Fornaro et al., 2014	Combination	46	Treatment-resistant depression	≥ 1 SSRI (Fava 2003)	HAM-D (21) ≥ 14	Adequate	Adequate	Not reported	MGHS	DSM-IV MDE with Atypical Features
45.	Frye et al., 2000	Monotherapy	31	Refractory	Not reported	Not reported	Not reported	Not reported	Not reported	No model	RDC or DSM-III-R unipolar depression or bipolar
46.	Garcia-Toro et al., 2001	TMS	40	Medication resistant	≥ 2 AD in current episode	Not reported	Maximum tolerated dose within therapeutic range	≥ 6 weeks	Not reported	No model	DSM-IV MDD
47.	Garcia-Toro et al., 2001	Monotherapy	20	Medication resistant	≥ 2 consecutive AD in current episode	Not reported	Maximum tolerated dose	≥ 6 weeks	Not reported	No model	DSM-IV MDD
48.	Garcia-Toro et al., 2006	TMS	30	Medication resistant	≥ 2 AD	Not reported	Maximum tolerated dose within therapeutic range	≥ 4 weeks	Not reported	No model	DSM-IV MDD
49.	Grunhaus et al., 2003	ECT vs. TMS	40	Treatment-resistant depression	≥ 1 AD	HAM-D (17) ≥ 18	Adequate levels as determined by MATS	≥ 4 weeks	Not reported	No model	DSM-IV MDD
50.	Harley et al., 2008	Psychotherapy	24	Treatment-resistant depression	≥ 1 AD	Not reported	Effective dose	≥ 6 weeks	Self-report	No model	DSM-IV MDD
51.	Heresco-Levy et al., 2006	Augmentation	22	Treatment-resistant depression	≥ 1 AD	HAM-D (21) ≥ 18	Not reported	≥ 4 weeks	Not reported	No model	DSM-IV MDD
52.	Heresco-Levy et al., 2013	Adjunctive	26	Treatment-resistant depression	≥ 2 AD	HAM-D (21) ≥ 20	Adequate	Adequate	Not reported	No model reported	DSM-IV recurrent MDD
53.	Hoencamp et al., 1994	Augmentation	51	Refractory	Did not lead to desired response	HAM-D (17) ≥ 14	Not reported	6 weeks	Plasma levels monitored	No model	DSM-III MDD (single or recurrent); DSM-III Bipolar (depressed); DSM-III Dysthyr with or without psychotic features

54.	Hopkinson & Kenny, 1975	Augmentation	14	Resistant to TCA	≥ 1 AD (TCA)	Exhibition of primary depressive features	150mg/day of a TCA	> 3 weeks	Not reported	No model	Depression as confirmed by consensus of opinion
55.	Ibrahim et al., 2012b	Ketamine	42	Treatment-resistant depression	≥ 2 AD	MADRS≥ 22	ATHF	ATHF	Not reported	No model	DSM-IV MDD recurrent without psychotic features
56.	Ibrahim et al., 2012a	Monotherapy	5	Treatment-resistant depression	≥ 2 AD in current episode	MADRS≥ 22	ATHF	ATHF	Not reported	No model	DSM-IV MDD
57.	Janicak et al., 2010	TMS	101	Pharmacoresistant MDD	≥ 1 AD but no more than 4 AD in current episode	HAM-D (17) ≥20	ATHF	ATHF	Not reported	No model	DSM-IV MDD
58.	Jarventausta et al., 2013	Adjunctive	32	Treatment-resistant depression	≥ 2 AD from 2 different classes	Not report	Max tolerated doses	≥ 6 weeks	Not reported	No model reported	DSM-IV recurrent severe or psychotic MDD
59.	Joffe et al., 1993	Augmentation	50	Refractory	1 AD (TCA)	HAM-D (17) ≥ 16	2.5mg/kg of body weight per day of TCA	5 weeks	Serum levels	No model	RDC MDD
60.	Katona et al., 1995	Augmentation	62	Failure to respond	1 AD (Fluoxetine or lofepramine)	HAM-D (17) ≥ 17	Not reported	Not reported	Not reported	No model	DSM-III MDD or DSM-III Bipolar (depressed phase)
61.	Kauffmann, Cheema & Miller, 2004	TMS	12	Medication resistant	≥ 2 AD	Not reported	Adequate doses	≥ 8 weeks	Not reported	No model	DSM-IV MDD
62.	Kayser et al., 2011	Magnetic Seizure Therapy	20	Treatment-resistant depression	≥ 2 AD from different classes in current episode	HAM-D (28) ≥ 20	Not reported	Not reported	Not reported	No model	DSM-IV MDD
63.	Kok et al., 2007	Augmentation	29	Treatment-resistant depression	≥ 1 AD either a TCA or Venlafaxine	MADRS≥ 20	Therapeutic dose and serum levels	≥ 4 weeks	Not reported	MGHS	DSM-IV MDD
64.	Landen et al., 1998	Augmentation	119	Treatment refractory	≥ 1 AD including Citalopram or Paroxetine	CGI ≥ 4	Equivalent to 40 mg/day citalopram and/or 30mg/day Paroxetine	≥ 4 weeks	Not reported	No model	DSM-IV MDE
65.	Lapidus et al., 2014	Ketamine	20	Treatment-resistant depression	≥ 1 AD	IDS-C ≥ 30	ATHF	ATHF	Not reported	No model reported	DSM-IV chronic or recurrent MDD without psychotic features
66.	Levkovitz et al., 2011	TMS	54	Treatment-resistant depression	Not reported	Not reported	Not reported	Not reported	Not reported	No model	Not reported
67.	Levkovitz et al., 2009	TMS	65	Treatment-resistant depression	≥ 2 AD in current episode	Not reported	Not reported	Not reported	Not reported	No model	Unipolar MDD

68.	Li et al., 2014	TMS	60	Treatment refractory	≥ 2 AD	CGI-S ≥ 4 + HAM-D (17) ≥ 18	Adequate	Adequate	Not reported	Maudsley Staging Model	DSM-IV recurrent MDD
69.	Loo et al., 1999	TMS	18	Resistant	Not reported	MADRS≥ 25	Not reported	Not reported	Not reported	No model	DSM-IV MDE
70.	Loo et al., 2003	TMS	19	Medication resistant	≥ 1 AD	MADRS≥ 25	Not reported	Not reported	Not reported	No model	DSM-IV MDE
71.	Maes, Vandoolaeghe & Desnyder, 1996	Augmentation	33	Treatment-resistant depression	≥ 2 AD from different classes	HAM-D (17) ≥ 18	Adequate dose	≥ 4 weeks	Not reported	Thase and Rush	DSM-III MDD
72.	Maes et al., 1999	Augmentation	31	Treatment-resistant depression	1 AD	HAM-D (17) ≥ 16	Not reported	Not reported	Not reported	Thase and Rush	DSM-III MDD
73.	Mahmoud et al, 2007	Augmentation	362	Treatment refractory	≥ 1 AD	CGI-S ≥ 4 and Carroll Depression Scale ≥ 20	Not reported	≥ 4 weeks	Not reported	No model	DSM-IV MDD
74.	Malison et al., 1999	Monotherapy	16	Treatment refractory	2 different AD or 1 AD with lithium augmentation	HAM-D (19) ≥ 17	Not reported	Not reported	Not reported	No model	DSM-III MDD
75.	Manes et al, 2001	TMS	20	Treatment refractory	≥ 1 AD	Not reported	Highest tolerated dose	≥ 4 weeks	Not reported	No model	DSM-IV MDE
76.	Marcus et al., 2008	Augmentation	381	Non-response to antidepressant therapy	≥ 1 AD but no more than 3 AD	HAM-D (17) ≥15 and CGI-I ≥ 4	ATFH	6 weeks	Not reported	No model	DSM-IV MDE
77.	Matthew et al., 2010	Ketamine	14	Treatment-resistant depression	≥ 2 AD in current episode	IDS-C ≥ 32	ATHF	ATHF	Not reported	No model	DSM-IV MDD
78.	Mazeh et al., 2007	Monotherapy	30	Resistant	2 AD in current episode	HAM-D (21) ≥ 18	20mg/day Fluoxetine and 150mg/day of Amitriyptline	8 weeks	Not reported	No model	DSM-IV MDD
79.	McDonald et al, 2006	TMS	62	Treatment-resistant depression	≥ 3AD in current episode	HAM-D (17) ≥20	Equivalent to 20mg/day Fluoxetine	6 weeks	Excluded if non-compliant	No model	DSM-IV MDD or DSM-IV Bipolar (Depressed phase)
80.	McGrath et al., 1993	Monotherapy	89	Treatment refractory	1 AD	Not reported	Not reported	Not reported	Not reported	No model	DSM-III MDD
81.	Miniussi et al., 2005	TMS	71	Drug resistant	≥ 2 AD from different classes	HAM-D (21) ≥ 12	Not reported	Not reported	Not reported	No model	DSM-IV MDD; DSM-IV Bipolar (depressed phase): DSM-IV Schizoaffective; DSM
82.	Miskowiak et al., 2014	Adjunctive	40	Treatment-resistant depression	≥ 2 AD from 2 different classes	HAM-D (17) ≥ 17	ATHF	ATHF	Assessed > 85% compliance	No model reported	DSM-IV MDD
83.	Moreno et al, 1997	Augmentation	10	Treatment-resistant depression	≥ 1 AD	HAM-D (25) ≥18	As per Thase and Rush	≥ 8 weeks	Not reported	Thase and Rush	DSM-III MDD
84.	Mosimann et al., 2004	TMS	24	Resistant	≥ 2 AD in current episode	Not reported	Adequate dose	Adequate duratio	Not reported	No model	DSM-IV MDD and ICD-10 Depression

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85.	Mota-Pereira et al., 2011	Physical Exercise	33	Treatment-resistant depression	≥ 2 AD	Not reported	APA guidelines	APA guidelines	Not reported	No model	DSM-IV MDD
86.	Mowla & Kardeh 2011	Augmentation	53	Resistant	1 AD (SSRI)	HAM-D (21) ≥ 18	Adequate dose	≥ 8 weeks	Not reported	No model	DSM-IV MDD
87.	Murrough et al., 2013	Ketamine	73	Treatment-resistant depression	≥ 3 AD	IDS-C ≥ 32	ATHF	ATHF	Not reported	No model reported	DSM-IV MDD
88.	Nahas et al., 2007	VNS	9	Treatment-resistant depression	≥ 2 AD but no more than 6 AD	Not reported	ATHF	ATHF	Not reported	No model	DSM-IV MDD or DSM-IV Bipolar I or II (depressed phase)
89.	Nelson et al., 2004	Combination	39	Resistant	≥ 1 AD	HAM-D (17) ≥ 18	Equivalent to 150mg/day Imipramine	≥ 4 weeks	Not reported	No model	DSM-IV MDD
90.	Nierenberg et al., 2003	Augmentation	92	Treatment-resistant depression	≥ 1 AD but no more than 5 AD	HAM-D (17) ≥18	ATHF	ATHF	Not reported	No model	DSM-III MDD
91.	Nolen et al., 1993	Monotherapy	22	Resistant to TCA	≥ 1 AD	HAM-D (17) ≥18	150mg of Nortripyline or 160mg Maproline	4 weeks	Plasma levels monitored	No model	DSM-III MDD
92.	Orengo, Fullerton & Kunik, 2005	Augmentation	18	Resistant	≥ 1 AD	HAM-D (21) ≥ 12	Appropriate dose	≥ 6 weeks	Not reported	No model	Not reported
93.	Padberg et al., 1999	TMS	18	Pharmacotherapy-refractory	≥ 2 AD including 1 TCA	Not reported	Adequate dose	≥ 4 weeks	Not reported	No model	DSM-IV MDD
94.	Padberg et al., 2002	TMS	31	Pharmacotherapy-resistant	≥ 2 AD	Not reported	Adequate dose	Adequate duration	Not reported	No model	DSM-IV MDD
95.	Pae et al., 2009	Augmentation	60	Treatment-resistant depression	≥ 1 AD	HAM-D (21) ≥ 15	Therapeutic dose	≥ 6 weeks	Not reported	No model	DSM-IV MDD
96.	Paillere Martinot et al., 2010	TMS	48	Medication resistant	≥ 2 AD from different classes	HAM-D (17) ≥ 16 and MADRS ≥ 21	Equivalent to > 150mg/day Imipramine	≥ 4 weeks	Not reported	No model	DSM-IV MDD
97.	Pallanti et al., 2010	TMS	60	Treatment-resistant depression	≥ 2 AD	HAM-D (not specified) ≥ 18	ATHF	ATHF	Not reported	Thase and Rush	DSM-IV MDD
98.	Palm et al., 2012	tDCS	22	Therapy resistance	≥ 2 AD from 2 different classes	Not report	ATHF	ATHF	Not reported	ATFH	DSM-IV MDE

99. Papakostas et al., 2010	Augmentation	73	SRI non-responders	≥ 1 AD but no more than 4 AD in current episode	HAM-D (not specified) ≥ 16	Equivalent to 20mg/day Fluoxetine/Citalopram/ Paraoxetine; 50mg/day Sertraline; 60mg/day Duloxetine; 150mg/day Venlafaxine	≥ 6 weeks	Not reported	No model	DSM-IV MDD
100. Papakostas et al., 2012	Adjunctive	148	SSRI resistance	≥ 1 AD but no more than 2 in current episode	QIDS-SR ≥ 12	Adequate	≥ 8 weeks	Not reported	Not reported	DSM-IV MDD
101. Pascual-Leone et al., 1996	TMS	17	Medication resistant	Resistant to multiple medications	Not reported	High dose	Not reported	Not reported	No model	DSM-III MDD
102. Patkar et al., 2006	Augmentation	60	Treatment-resistant depression	≥ 1 AD	HAM-D (21) ≥ 15	Therapeutic dose	≥ 6 weeks	Not reported	No model	DSM-III MDD
103. Perez et al., 1999	Augmentation	88	Resistant	≥ 1 AD	HAM-D (17) ≥16	Equivalent to SSRIs: Fluoxetine 40mg/d; Fluvoxamine 200mg/d; Paroxetine 40mg/d; non-selective 5-HT reuptake inhibitor Clomipramine 150mg/d.	≥ 6 weeks	Serum levels	Thase and Rush	DSM-IV MDD
104. Perry et al., 2004	Augmentation	42	Resistant	1 AD (Fluoxetine or Paraoxetine or Sertraline)	HAM-D (25) ≥25	At least 20mg/day Fluoxetine; 20mg/day Paraoxetine; 50mg/day Sertraline	≥ 6 weeks	Not reported	No model	DSM-IV MDE
105. Poirier & Boyer, 1999	Monotherapy	123	Treatment-resistant depression	2 consecutive AD in the current episode	HAM-D (17) ≥18 and CGI-I ≥ 3	Effective dose equivalent to 100 – 150mg of Clomipramine	≥ 4 weeks	Not reported	No model	DSM-III MDE
106. Pope et al., 2003	Augmentation	22	Refractory	1 AD	Not reported	Adequate dose	≥ 4 weeks	Not reported	No model	DSM-IV MDD
107. Price et al., 1990	Augmentation	15	Tricyclic refractory	≥ 1 AD (TCA)	Not reported	2.5mg/kg of body weight per day of TCA	≥ 4 weeks	Plasma levels monitored	No model	DSM-III MDD
108. Price et al., 2014	Ketamine	57	Treatment-resistant depression	≥ 3 AD	IDS-C ≥ 32	ATHF	ATHF	Not reported	Not reported	DSM-IV MDD
109. Price et al., 2010	TMS	44	Treatment refractory	≥ 1 AD	Not reported	Self-report	Self-report	Not reported	No model	DSM-IV MDD

110. Pridmore et al., 2000	ECT vs. TMS	22	Medication resistant	≥ 2 families of AD	MADRS > 26 and HAM-D (17) > 18	Maximum recommended dose	> 4 weeks	Not reported	No model	DSM-IV MDD
111. Quante et al., 2011	ECT	41	Resistant	≥ 2 consecutive AD	Not reported	ATHF	ATHF	Not reported	No model	DSM-IV MDD or DSM-IV Bipolar I or II (depressed phase)
112. Raison et al., 2013	TNF infusions	60	TRD	MGHS score of 2 or above	QIDS-SR ≥ 14	MGHS	MGHS	Not reported	MGHS	DSM-IV MDD
113. Rapaport et al., 2006	Augmentation	489	Treatment-resistant depression	≥ 1 AD but no more than 3 AD in the current episode	HAM-D (17) > 20	Dose approved by the FDA	≥ 6 weeks	Not reported	No model	DSM-IV MDD
114. Reimherr et al., 2010	Augmentation	261	Treatment-resistant depression	Not reported	HAM-D (17) > 18	Equivalent to maximum dose of 200mg of Sertraline	8 weeks	Not reported	No model	DSM-IV MDD
115. Rosa et al., 2006	ECT vs. TMS	42	Refractory	≥ 2 AD of different classes with augmentation of either lithium or thyroid hormone for at least 1 trial	HAM-D (17) ≥ 22	Adequate dose	≥ 4 weeks	Not reported	No model	DSM-IV MDD
116. Rossini et al., 2005	TMS	54	Resistant	≥ 2 AD from different classes in current episode	HAM-D (21) ≥ 26	Adequate dose	≥ 6 weeks	Not reported	No model	DSM-IV MDD or DSM-IV Bipolar I or II (depressed phase)
117. Rosso et al., 2012	Monotherapy	49	SSRI resistant	2 AD (SSRI)	HAM-D (17) ≥ 18	Therapeutic dose	≥ 4 weeks	Not reported	No model	DSM-IV MDE
118. Rush et al., 2005	VNS	235	Treatment-resistant depression	≥ 1 AD but no more than 6 AD in the current episode	HAM-D (24) ≥ 20	ATHF and ARR	ATHF and ARR	Not reported	No model	DSM-IV MDD or DSM-IV Bipolar I or II (depressed phase)
119. Rybakowski et al., 1999	Augmentation	59	Treatment-resistant depression	2 AD	HAM-D (17) ≥ 18	Adequate dose	≥ 4 weeks	Not reported	Thase and Rush	ICD-10 Depression and DSM-IV MDD
120. Sackeim et al., 2001	Augmentation	84	Medication resistant	≥ 1 AD	HAM-D (24) ≥ 21	ATHF	ATHF	Excluded if non-compliant	No model	SADS
121. Salehi et al., 2014	Adjunctive	60	TR-MDD	Not reported	BDI ≥ 30 + HAM-D ≥ 25	Appropriate	6 to 8 months	Not reported	Not reported	DSM-IV MDD
122. Santos, Rocha & Hara, 2008	Augmentation	34	Treatment-resistant depression	≥ 2 AD of different classes	Moderate to severe intensity	Maximum tolerated dose	≥ 6 weeks	Not reported	Thase and Rush	DSM-IV MDD

123. Schnindler & Anghelescu, 2007	Augmentation	34	Treatment-resistant depression	≥ 2 AD of different classes	HAM-D (17) ≥ 17	Not reported	≥ 6 weeks	Not reported	No model	DSM-IV MDD
124. Seidman, Miyazaki & Roose, 2005	Augmentation	26	Treatment-resistant depression	2 AD	HAM-D (24) ≥ 12	Adequate dose	≥ 6 weeks	Not reported	No model	DSM-IV MDD
125. Shapira et al., 1996	ECT	47	Medication resistant	Not reported	HAM-D (21) ≥ 18	ATHF	ATHF	Not reported	No model	RDC MDD
126. Shelton et al., 2001	Augmentation	28	Treatment-resistant depression	2 AD of different classes one which is not an SSRI	HAM-D (21) ≥ 20	Therapeutic dose	≥ 4 weeks	Not reported	No model	DSM-IV MDD
127. Shelton et al., 2005	Combination	500	Treatment-resistant depression	≥ 1 AD including SSRI	MADRS ≥ 20	Therapeutic dose	≥ 4 weeks	Self-report	No model	DSM-IV MDD
128. Siwek et al., 2009	Augmentation	60	Resistant	As per Thase and Rush Model	Not reported	Not reported	Not reported	Not reported	Thase and Rush	DSM-IV MDD
129. Sobis et al., 2010	Magnetic field stimulation	30	Resistant	≥ 2 AD of different classes	HAM-D (21) ≥ 18	High dose	≥ 6 weeks	Not reported	No model	DSM-IV MDD
130. Sokolski et al., 2004	Augmentation	9	SSRI-refractory	≥ 2 AD	HAM-D (not specified) > 21	Adequate dose	≥ 8 weeks	Not reported	No model	DSM-IV MDD
131. Sourey et al., 2011	Switching	189	Treatment-resistant depression	≥ 1 AD (not Citalopram or Desimpramine)	HAM-D (17) ≥ 17	Adequate dose	≥ 4 weeks	Not reported	No model	DSM-IV MDE
132. Speer et al., 2009	TMS	22	Refractory	Not reported	Not reported	Not reported	Not reported	Not reported	No model	DSM-IV MDD or DSM-IV Bipolar I or II (depressed phase)
133. Speer et al., 2013	TMS	24	Treatment-resistant depression	≥ 2 AD	Not report	Not reported	not reported	Not reported	Not reported	DSM-IV MDE'
134. Straaso et al., 2014	Augmentation	34	Treatment-resistant depression	> 3 on the Sackheim Scale	HAM-D (17) ≥ 13	ATHF	ATFH	Not reported	ATHF	DSM-IV MDD
135. Su, Huang & Wei, 2005	TMS	30	Medication resistant	≥ 2 AD	HAM-D (21) ≥ 18	Adequate dose	≥ 6 weeks	Not reported	No model	DSM-IV MDE
136. Sunderland et al., 1994	Monotherapy	16	Resistant	≥ 2 AD	HAM-D (17) ≥ 18	Not reported	Not reported	Not reported	No model	DSM-III MDD
137. Thase et al., 2002	Switching	168	Antidepressant non-responders	≥ 2 AD from different classes	CGI-I ≥ 3 and HAM-D (24) ≥ 18	Maximum dose tolerated	6 weeks	Not reported	Thase and Rush	DSM-III MDD
138. Thase et al., 2007	Combination	605	Treatment-resistant depression	Documented history of current episode AD failure plus prospective	HAM-D (17) ≥ 22	Therapeutic dose	6 weeks	Not reported	No model	DSM-IV MDD

				failure of Fluoxetine						
139. Triggs et al., 2010	TMS	48	Resistant	≥ 2 AD from different classes (at least one was SSRI)	HAM-D (24) ≥ 18	Therapeutic dose	≥ 4 weeks	Not reported	No model	DSM-IV MDD
140. Turnier-Shea, Bruno & Pridmore, 2006	TMS	16	Treatment-resistant depression	≥ 2 AD	HAM-D (17) ≥ 18	Maximum dose	≥ 4 weeks	Not reported	No model	DSM-IV MDD
141. van den Broek et al., 2006	Monotherapy	27	Pharmacotherapy treatment failure	1 AD and subsequent lithium addition and/or MAOI	Not reported	Adequate plasma levels	4 weeks	Not reported	No model	DSM-IV MDD
142. Watkins et al., 2011	Psychotherapy	42	Refractory	Not reported	HAM-D (17) ≥18 and BDI-II ≥ 9	Therapeutic dose	≥ 8 weeks	Not reported	No model	DSM-IV MDD
143. Wiles et al., 2008	Psychotherapy	23	Treatment-resistant depression	Non response to AD	BDI-II ≥ 15	Not reported	Not reported	Morisky Scale	No model	ICD-10 Depression
144. Wiles et al., 2013	Psychotherapy	469	Treatment-resistant depression	≥ 1 AD	BDI ≥ 14	Adequate	≥ 6 weeks	Not reported	British National Formulary and advice from psychopharmacology experts	ICD-10 Depression
145. Zarate et al., 2006	Monotherapy	18	Treatment-resistant depression	≥ 2 AD	HAM-D (21) ≥ 18	ATHF	ATHF	Not reported	No model	DSM-IV MDD
146. Zarate et al., 2013	N-methyl-D-aspartate (NMDA) Channel Blocker	22	Treatment-resistant depression	≥ 2 AD	MADRS ≥ 20	ATHF	ATHF	Not reported	Not reported	DSM-IV MDD
147. Zusky et al., 1988	Augmentation	18	Resistant	≥ 1 AD	HAM-D (not spec) ≥ 12	Highest tolerated dose	≥ 4 weeks	Not reported	No model	DSM-III MDD

Appendix 3. Ethical and administrative approvals for research

Approval to conduct research onsite at New Farm Clinic

People caring for people

NEW FARM CLINIC

New Farm Clinic
ABN 28 010 219 628
22 Sargent Street
New Farm QLD 4005
Telephone: (07) 3254 9100
Facsimile: (07) 3358 4781

29 April 2013

Jennifer Murphy
109 Jubilee Terrace
Bardon 4065

Dear Jennifer,

I am writing to confirm the New Farm Clinic Medical Advisory Committee granted approval for you to approval conduct research for your thesis, at New Farm Clinic, on the 1st March 2011.

Yours sincerely

Kenneth Craig
Chief Executive Officer
New Farm Clinic

University of Queensland Medical Research Ethics Committee approvals

THE UNIVERSITY OF QUEENSLAND
Institutional Approval Form For Experiments On Humans Including Behavioural Research

Chief Investigator:	Ms Jenifer Murphy
Project Title:	Persistent Depression
Supervisor:	A/Prof Gerard Byrne, A/Prof Nancy Pachana
Co-Investigator(s)	None
Department(s):	School of Medicine
Project Number:	2010000124
Granting Agency/Degree:	Sylvia Bligh Memorial Scholarship
Duration:	31st December 2013

Comments:

Expedited review on the basis of secondary data analysis of public domain ABS data.

Name of responsible Committee:-
Behavioural & Social Sciences Ethical Review Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:-
Dr John McLean
Acting Chairperson
Behavioural & Social Sciences Ethical Review Committee

Date 5/02/2010 Signature

THE UNIVERSITY OF QUEENSLAND

Institutional Approval Form For Experiments On Humans Including Behavioural Research

Chief Investigator:	Ms Jenifer Murphy
Project Title:	Factors Associated With Treatment Outcomes In Major Depressive Disorder
Supervisor:	A/Prof Gerard Byrne, A/Prof Nancy Pachana
Co-Investigator(s):	None
Department(s):	School of Medicine - Dept of Psychiatry
Project Number:	2010001485
Granting Agency/Degree:	PhD Scholarship - Sylvia Bligh Memorial Scholarship
Duration:	31st December 2013

Comments:

Name of responsible Committee:-
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:-
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Date: 21.11.2011 Signature: _____

Appendix 4. Publication incorporated into Chapter Three and Four

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Research report

Prevalence and correlates of the proposed DSM-5 diagnosis of Chronic Depressive Disorder

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ABSTRACT

Context: The draft proposal to add Chronic Depressive Disorder to DSM-5 will combine DSM-IV Dysthymic Disorder and Major Depressive Disorder, with chronic specifier, into a single diagnosis.
Objective: The objective of this study is to estimate the prevalence and correlates of the proposed DSM-5 diagnosis of Chronic Depressive Disorder using unit record data from the 2007 Australian National Survey of Mental Health and Wellbeing.
Design: Secondary analysis of a nationally representative household survey.
Setting: Urban and rural census tracts.
Participants: One individual between the ages of 16 and 85 years from 8841 households was interviewed for the survey.
Main outcome measure: Lifetime prevalence estimates for chronic and non-chronic depression were determined using data from the World Health Organization's Composite International Diagnostic Interview, version 3.0 (WMH-CIDI 3.0).
Results: Chronic depression of at least two years' duration had a lifetime prevalence of 4.6% (95% CI: 3.9–5.3%) and was found in 29.4% (95% CI: 25.6–33.3%) of individuals with a lifetime depressive disorder. Higher rates of psychiatric co-morbidity (OR = 1.42; 95% CI = 1.26–1.61), older age (OR = 1.04; 95% CI = 1.02–1.05), a younger age of onset (OR = 0.97; 95% CI = 0.95–0.98) and more frequent episodes of depression (OR = 1.75; 95% CI = 1.07–2.86) were found to be significant correlates of chronic depression. The first episode of depression for individuals with chronic depression often developed after the death of someone close (OR = 2.38; 95% CI 1.16–5.79).
Conclusions: Chronic depression is highly prevalent among community-residing persons and has a set of correlates that discriminate it from non-chronic depression. The distinction between chronic and non-chronic depression proposed for DSM-5, in the form of Chronic Depressive Disorder, seems to be warranted.

1. Introduction

The draft version of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) outlines proposed criteria for the new diagnosis of Chronic Depressive Disorder (APA, 2010). This new diagnosis encompasses DSM-IV Dysthymic Disorder and those cases of Major Depressive Disorder (MDD) with chronic specification (APA, 1994). Chronic Depressive Disorder has been proposed for DSM-5 in response to research findings highlighting the homogeneous nature of the various types of chronic depressive states (APA, 2010). In particular, it is now argued that Dysthymic Disorder, MDD with chronic specification, and so-called double depression (combined MDD and Dysthymic Disorder) cannot be satisfactorily differentiated, either clinically or

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etiologically (Klein, 2008; McCullough et al., 2003; Rhebergen et al., 2009). The proposed diagnostic criteria for DSM-5 Chronic Depressive Disorder are summarized in Table 1.

Although Dysthymic Disorder, MDD with chronic specification, and double depression may not vary enough from each other to warrant their continuation as distinct disorders, they do appear to vary significantly from non-chronic MDD (Klein, 2008; Klein et al., 2006; McCullough et al., 2003; Rhebergen et al., 2009). In comparison with non-chronic MDD, the chronic depression sub-types have different disease courses, lower response rates to treatment, higher rates of family history and more psychiatric co-morbidity (Alnaes and Torgersen, 1997; Angst et al., 2009; Klein et al., 2006; McCullough et al., 2003; Mondimore et al., 2007). The distinction between chronic and non-chronic depression is stable over time with chronic individuals being fourteen times more likely than non-chronic individuals to have a chronic presentation ten years later (Klein et al., 2006). It has been argued that the distinction between chronic and non-chronic depression may be more clinically and etiologically relevant than any of the distinctions between the various sub-types and manifestations of chronic depression as they are represented in DSM-IV (Klein et al., 2006; McCullough et al., 2003; Mondimore et al., 2007).

As expected, chronic depressive disorders have been associated with a slower rate of improvement over time and a poorer response to treatment in comparison with non-chronic MDD (Klein et al., 2006) In addition, longer episode durations with fewer lifetime episodes (Gilmer et al., 2005; Rush et al., 1995) and higher rates of suicidal ideation have been associated with chronic depression (Satyanarayana et al., 2009). Chronicity has also been linked to a wide range of factors, including the following: higher rates of family history of mood disorder (Mondimore et al., 2007); early childhood trauma or adversity (Gopinath et al., 2007; Honkalampi et al., 2005; Wiersma et al., 2009); a negative cognitive style (Riso et al., 2003); higher rates of medical and psychiatric co-morbidity (Gilmer et al., 2005; Satyanarayana et al., 2009; Viinamaki et al., 2006); older age (Gilmer et al., 2005; Rush et al., 1995); less education (Gilmer et al., 2005); lower socioeconomic status (Gilmer et al., 2005); lack of health insurance (Gilmer et al., 2005); and a rural place of residence (Viinamaki et al., 2006). Also associated with a more chronic course of depression are greater levels of disability (Ormel et al., 2004; Satyanarayana et al., 2009), poor subjective health (Honkalampi et al., 2005), insufficient social support (Honkalampi et al., 2005) and lower self-efficacy (Gopinath et al., 2007). However, these latter factors might be consequences rather than causes of chronicity.

Much of what is known about the sociodemographic and clinical correlates of chronic depression has come from studies of ambulatory clinic populations. Very few population-based community studies have investigated chronic depression, and as a consequence, available research findings might not generalize well to the population at large. One US community-based epidemiological study estimated that the prevalence of persistent depression in the general population is 3.4% (Young et al., 2008). A recent Canadian study, based on a national population-based survey, found that those with chronic depression represented 26.8% of all individuals with MDD and that chronicity was associated with higher rates of psychiatric and medical co-morbidity, greater disability, increased health service use and higher rates of suicidal ideation and attempts (Satyanarayana et al., 2009). The Netherlands Mental Health Survey and Incidence Study (NEMESIS), an earlier community-based study, estimated that 20% of those with depression had a more chronic course (Spijker et al., 2002).

As the draft DSM-5 begins to explicitly acknowledge the distinction between chronic and non-chronic depressive states and there is increased recognition of the magnitude of the public health burden associated with depression

Table 1
Comparison of diagnostic criteria for DSM-IV Dysthymic Disorder and proposed DSM-5 Chronic Depressive Disorder.

Proposed DSM-5 Chronic Depressive Disorder	DSM-IV Dysthymic Disorder
A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years.	A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years.
B. Presence, while depressed, of two (or more) of the following:	B. Presence, while depressed, of two (or more) of the following:
1. Poor appetite or overeating	1. Poor appetite or overeating
2. Insomnia or hypersomnia	2. Insomnia or hypersomnia
3. Low energy or fatigue	3. Low energy or fatigue
4. Low self esteem	4. Low self esteem
5. Poor concentration or difficulty making decisions	5. Poor concentration or difficulty making decisions
6. Feelings of hopelessness	6. Feelings of hopelessness
C. During the 2-year period of the disturbance, the person has never been without the symptoms in Criteria A and B for more than 2 months at a time.	C. During the 2-year period of the disturbance, the person has never been without the symptoms in Criteria A and B for more than 2 months at a time.
D. The disturbance does not occur exclusively during the course of a chronic Psychotic Disorder, such as Schizophrenia or Delusional Disorder.	D. No Major Depressive Episode has been present during the first 2 years of the disturbance, i.e. the disturbance is not better accounted for by chronic Major Depressive Disorder, or Major Depressive Disorder, In Partial Remission.
G. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, medication) or general medical condition (e.g. hypothyroidism)	E. There has never been a Manic episode, a Mixed episode or a Hypomanic episode, and criteria have never been met for Cyclothymic Disorder.
H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	F. The disturbance does not occur exclusively during the course of a chronic Psychotic Disorder, such as Schizophrenia or Delusional Disorder.
	G. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, medication) or general medical condition (e.g. hypothyroidism)
	H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

(Murray and Lopez, 1996), it is timely to explore the prevalence and correlates of chronic depression in the community. Accordingly, we investigated the prevalence and correlates of chronic depression in an Australian population-based sample of community-residing individuals.

2. Methods

2.1. National survey

The second National Survey of Mental Health and Wellbeing (NSMHWB) was conducted by the Australian Bureau of Statistics (ABS) during 2007 and was designed to investigate high-prevalence mental health disorders in community-residing Australians (Australian Bureau of Statistics, 2007). The design of the 2007 NSMHWB has been described in detail elsewhere (Slade et al., 2009). In brief, households from Australian states and territories were selected at random using a stratified, multistage, area sampling method with a response rate of approximately 60%. All participants gave informed consent. One individual between the ages of 16 and 85 years from each of 8841 households was interviewed using the World Mental Health Survey Initiative version of the World Health Organization's Composite International Diagnostic Interview, version 3.0 (WMH-CIDI 3.0) (Kessler and Ustun, 2004). Selected parts of the WMH-CIDI 3.0, which is based on international survey modules, were adapted for use with this Australian sample. Young people and older people were over-sampled to improve standard errors.

2.2. Sample selection

Of the 8841 individuals interviewed, 1366 (15.1%; 95% CI: 14.1%–16.0%) were assigned a lifetime DSM-IV diagnosis of either Major Depressive Disorder (MDD) or Dysthymic Disorder, or both. There were 229 individuals who met criteria for both a lifetime diagnosis of MDD and a lifetime diagnosis of Dysthymic Disorder and 25 individuals who had only a diagnosis of Dysthymic Disorder. The remaining 1112 individuals in the depressed sub-sample had a lifetime diagnosis of MDD, with no Dysthymic Disorder. It should be noted that one individual with MDD was excluded from the analysis due to missing data on episode duration and persistence variables. Individuals with a history of Bipolar Disorder were not excluded from the study.

2.3. Classification of cases

All individuals with a lifetime diagnosis of Dysthymic Disorder (N = 254) were classified as having chronic depression. To identify which of the 1111 individuals with MDD but no Dysthymic Disorder had a chronic course of depression, the duration or persistence of symptoms was used as the indicator of chronicity. The WMH-CIDI 3.0 assessed persistence of MDD by asking individuals to recall their worst episode of being "sad or discouraged or uninterested" when they also had "the largest number of other problems". The "largest number of other problems" referred to the subjects' previously reported depressive symptoms, including problems with appetite, sleep and concentration. The diagnostic interview also assessed how old the person was at the start of the episode and the duration of the episode. For the purposes of this analysis, and in line with the duration criterion in the proposed DSM-5 Chronic Depressive Disorder, individuals who had a lifetime diagnosis of MDD and who had a persistence of two years or more were defined as chronic (N = 144) and those with a persistence of less than two years were defined as non-chronic (N = 967). Using this approach, participants were divided into two groups, those with chronic depression (i.e., those with MDD and persistence equal to or greater than two years and those with Dysthymic Disorder; N = 398; coded 1) and those with non-chronic depression (i.e., those with MDD and persistence less than two years; N = 967; coded 0).

2.4. Putative correlates

Putative correlates, including age, gender, employment status, age of onset and number of depressive episodes, were assessed by the WMH-CIDI 3.0 interviewer and relied on participant recall. Suicidal ideation was measured with a dichotomous item asking whether the individual had ever thought about committing suicide during their worst "sad/discouraged/uninterested" episode. Symptom severity was assessed by asking participants to rate the severity of their emotional distress on a four-point scale (mild/moderate/severe/very severe) during their worst episode.

Current psychological distress was measured on the 10-item Kessler Psychological Distress Scale (K-10), with higher scores indicating higher levels of psychological distress (minimum score, 10; maximum score, 50) (Kessler et al., 2002). Current disability was measured on the 12-item World Health Organization Disability Assessment Schedule (WHODAS II), with higher scores indicating higher levels of disability (minimum score, 0; maximum score, 100) (World Health Organization, 2001). Psychiatric co-morbidity was estimated by counting the total number of lifetime DSM-IV disorders detected by the WMH-CIDI 3.0 interview (min score, 1; max score, 11). Family history was measured by asking participants how many first-degree relatives they had with depression. Medical co-morbidity was estimated by counting the total number of chronic medical conditions reported by each participant (minimum score, 0; maximum score, 11). Traumatic load was estimated by counting the total number of lifetime traumatic events reported by each participant (minimum score, 0; maximum score, 29). The hopelessness and worthlessness measures were self-reported items of the K-10 (minimum score, 1 = none of the time; maximum score, 5 = all of the time).

2.5. Statistical analyses

Data analyses were conducted in Stata 11 (StataCorp, 2009) using survey data routines. Individualized person weights were used to allow population estimates to be calculated. Standard errors of prevalence estimates and confidence intervals around odds ratios were calculated on the basis of delete-one jackknife replications using 60 replicate weights provided by the ABS. This approach was necessary because of the confidentialized nature of the unit record data set. The prevalence estimates reported take into account the probability of being sampled and have been standardized to the projected 2007 age and sex distribution of the Australian

Table 2
Sociodemographic and clinical features associated with chronic and non-chronic depression.

Feature	Non-chronic (N = 967) N (%)/Mean ± SD	Chronic (N = 398) N (%)/Mean ± SD	OR	95% CI	t	p
Age (years)	43.07 ± 15.84	47.24 ± 15.38	1.01	1.00–1.02	3.07[a]	<.003
Gender						
Female	628 (64.94)	262 (65.83)				
Male	339 (35.06)	136 (34.17)	1.00	.72–1.39	.02	.982
Education						
Tertiary	409 (42.30)	130 (32.66)				
High school level	369 (38.16)	196 (49.25)	1.63	1.11–2.41	2.53	.014
Skilled vocation	189 (19.54)	72 (18.09)	1.28	.79–2.07	1.01	.315
Employment status						
Employed	651 (67.32)	209 (52.51)				
Unemployed	316 (32.68)	189 (47.49)	2.09	1.44–3.03	3.97[a]	<.001
Number of episodes						
Fewer no. of episodes (≤3)[b]	663 (69.86)	158 (43.05)				
Greater no. of episodes (>3)[b]	286 (30.14)	209 (56.95)	3.24	2.17–4.85	5.84[a]	<.001
Age of onset (years)	29.37 ± 14.66	25.35 ± 14.43	.98	.96–.99	−3.40[a]	<.001
Symptom severity						
Non-severe symptoms	316 (32.68)	82 (20.60)				
Severe symptoms	651 (67.32)	316 (79.40)	1.79	1.16–2.76	2.67	.010
No. of family members with depression	.41 ± .71	.62 ± .91	1.23	.97–1.55	1.75	.086
Suicidal ideation						
No	575 (59.46)	177 (44.58)				
Yes	392 (40.54)	220 (55.42)	1.69	1.11–2.58	2.49	.016
Previous suicide attempt(s)						
No	849 (87.80)	315 (79.35)				
Yes	118 (12.20)	82 (20.65)	1.78	1.14–2.76	2.61	.011
No of. co-morbid psychiatric disorders	2.62 ± 1.67	4.11 ± 2.18	1.48	1.34–1.63	8.17[a]	<.001
No of. co-morbid medical conditions	2.17 ± 1.98	3.03 ± 2.50	1.18	1.09–1.27	4.47[a]	<.001
Traumatic load	3.06 ± 2.77	4.13 ± 3.27	1.12	1.05–1.19	3.41[a]	<.001
Current disability (WHODAS12)	12.57 ± 13.83	20.83 ± 18.83	1.03	1.02–1.04	6.50[a]	<.001
Current psychological distress (K-10)	18.11 ± 6.58	21.92 ± 8.86	1.06	1.03–1.08	5.01[a]	<.001
Precipitating factor to first episode						
Out of the blue	116 (12.00)	48 (12.09)				
Death of someone close	200 (20.68)	79 (19.90)	1.32	.74–2.35	.96	.342
Stress	651 (67.32)	270 (68.01)	1.00	.58–1.70	−.02	.988

Abbreviations: OR = odds ratio; CI = confidence interval; SD = standard deviation; Coding: chronic (1.00) non-chronic (0.00).
[a] Significant finding after Bonferroni adjustment.
[b] Missing data on variable due to participants not reporting number of episodes of depression.

population based on the 2006 population census (Australian Bureau of Statistics, 2007).

The lifetime prevalence of co-morbid disorders was estimated controlling for respondent age at time of interview. The temporal relationships between chronic and non-chronic depression and lifetime co-morbidity were investigated using retrospective age of onset reports, which were graphed using discrete-time survival analyses with person–year as the unit of analysis. The method of using person–year as the unit of analysis for survival analysis is described elsewhere (Nock et al., 2009).

Putative factors associated with chronic depression that were identified in the research literature and factors found in bivariate analyses with $p < .01$ were included in a multivariable logistic regression model. Some variables were collapsed into fewer categories due to the presence of redundant categories or for ease of interpretation. In particular, symptom severity was dichotomized into non-severe and severe symptoms and number of episodes was dichotomized into either three or fewer episodes or four or more episodes. Descriptive statistics for the variables used in the multivariable model are presented in Table 2.

Wald chi-square tests (χ^2) were used to test the significance of each coefficient in the final model. The Hosmer–Lemeshow test was used to assess the goodness-of-fit of the final model.

3. Results

3.1. Prevalence and sociodemographic correlates

Chronic depression (CD), which included 229 individuals with both a lifetime diagnosis of MDD and a lifetime diagnosis of Dysthymic Disorder, 25 individuals with only Dysthymic Disorder and 144 individuals with persistent/chronic MDD was present in 29.4% (95% CI: 25.6%–33.3%) of all individuals with a lifetime depressive disorder (MDD and/or Dysthymic Disorder). The population-weighted estimate of the lifetime prevalence of chronic depression in community-residing persons was 4.6% (95% CI: 3.9–5.3%), with non-chronic depression (NCD) having an estimated lifetime prevalence of 10.4% (95% CI: 9.6–11.2%).

Socio-demographic and clinical comparisons between individuals with CD and NCD are summarized in Table 2. As

Table 3
Lifetime co-morbid diagnoses for individuals with chronic and non-chronic depression.

Co-morbid disorder	Lifetime prevalence of co-morbidity[a]						Temporal relationship between onset of chronic/non-chronic depression and co-morbidities[a]					
							Chronic depression (N=398)			Non-chronic depression (N=967)		
	Non-chronic (N=967) N (%)	Chronic (N=398) N (%)	OR	95% CI	t	p	CD first N (%)	Other disorder first N (%)	Same year N (%)	NCD first N (%)	Other disorder first N (%)	Same year N (%)
Post traumatic stress	201 (20.79)	133 (33.42)	2.16	1.57–2.98	4.78 [b]	<.001	68 (51.13)	45 (33.83)	20 (15.04)	67 (33.33)	94 (46.77)	40 (19.90)
Agoraphobia	44 (4.55)	37 (9.30)	1.84	1.01–3.36	2.03	.047	8 (21.62)	15 (40.54)	14 (37.84)	10 (22.72)	25 (56.82)	9 (20.45)
Social phobia	255 (26.37)	152 (38.19)	1.58	1.06–2.36	2.32	.024	27 (17.76)	99 (65.13)	26 (17.11)	28 (10.98)	192 (75.29)	35 (13.73)
Panic	107 (11.07)	67 (16.83)	1.62	.99–2.65	1.94	.057	24 (35.82)	21 (31.34)	22 (32.84)	19 (17.76)	38 (35.51)	50 (46.73)
Generalized anxiety	239 (24.72)	220 (55.28)	3.43	2.41–4.87	7.01 [b]	<.001	83 (37.73)	58 (26.36)	79 (35.91)	64 (26.78)	77 (32.22)	98 (41.00)
Obsessive–compulsive	89 (9.20)	48 (12.06)	2.29	1.37–3.82	3.24 [b]	<.002	17 (35.42)	22 (45.83)	9 (18.75)	31 (34.83)	45 (50.56)	13 (14.61)
Bipolar I	33 (3.41)	21 (5.28)	1.57	.57–4.33	.88	.381	14 (66.67)	3 (14.29)	4 (19.05)	20 (60.61)	4 (12.12)	9 (27.27)
Bipolar II	32 (3.31)	19 (4.77)	1.51	.52–4.45	.77	.444	10 (52.63)	3 (15.79)	6 (31.58)	18 (56.25)	6 (18.75)	8 (25.00)
Substance abuse	79 (8.17)	36 (9.05)	1.00	.58–1.74	.01	.992	24 (66.67)	10 (27.78)	2 (5.56)	27 (34.18)	41 (51.90)	11 (13.92)
Substance dependence	131 (13.55)	74 (18.59)	1.04	.65–1.68	.18	.859	42 (56.76)	25 (33.78)	7 (9.46)	45 (34.35)	69 (52.67)	17 (12.98)

Abbreviations: OR=odds ratio; CI=confidence interval; Coding: chronic (1.00) non-chronic (0.00).
[a] Adjusted for age at interview.
[b] Significant finding after Bonferroni adjustment.

expected in a sample of depressed individuals, females outnumbered males in both groups. In comparison with NCD individuals, those with CD were older and more likely to be unemployed.

3.2. Clinical features

Individuals with CD had a younger age of onset and more frequent episodes of depression compared to NCD individuals. Individuals with CD also had higher levels of disability, more traumatic events experienced in their lifetime, more chronic medical conditions and higher psychological distress compared to individuals with NCD. Table 2 displays the clinical features associated with CD.

3.3. Psychiatric co-morbidity

The CD sample had a greater number of lifetime co-morbid psychiatric disorders than NCD individuals (see Table 2). In particular, CD individuals had significantly higher rates of post-traumatic stress disorder, generalized anxiety disorder and obsessive–compulsive disorder (see Table 3). Chi-square analyses determined no significant differences between the two groups in terms of the temporal sequence of the development of the co-morbid disorders and their depression (see Table 3). The onset of CD and the development of lifetime DSM-IV co-morbid disorders are depicted in Fig. 1.

3.4. Health service utilization

During their lifetime, 70.9% of individuals with CD (N=282) and 64.4% of those with NCD (N=623) had consulted a general practitioner (GP; primary care physician) about their mental health problems (OR=1.21; 95% CI 0.73–1.71). There was no significant difference between the two groups on whether they had consulted a general practitioner (GP; primary care physician) about their mental health problems. Individuals with CD (40.7%; N=162) were more likely to have had a consultation with a psychiatrist during their lifetime compared with non-chronic individuals (25.5%; N=247) (OR=1.62; 95% CI 1.11–2.38). However, 42.2% of CD individuals (N=168) and 59.4% of NCD individuals (N=574) believed that they had no need to utilize the mental health services that were available to them. After adjusting for chronicity, no difference was found between individuals who felt they had no need to utilize services and individuals who did feel the need to access services on their self-reported hopelessness score (OR=.82; 95% CI .64–1.06; t=−1.56; p=.125). On their self-reported worthlessness score, adjusting for chronicity, individuals who felt no need to access services had a significantly lower worthlessness score than individuals who felt the need to access services (OR=.65; 95% CI: .51–.84; t=−3.40; p<.001).

3.5. Correlates of chronic depression

Fifteen putative correlates of chronic depression were entered into a multivariable logistic regression model (see Table 4). The goodness-of-fit of the multivariable model was tested with the Hosmer–Lemeshow statistic and found

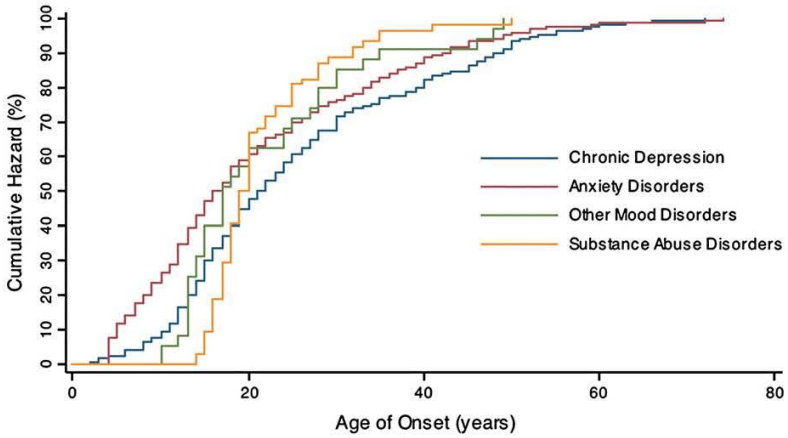

Fig. 1. The age of onset of chronic depression (N = 398) and lifetime DSM-IV co-morbid mental disorders.

to be satisfactory ($\chi^2 = 3.89$, df = 8, p = 0.87). The model correctly classified 77.3% of individuals with a sensitivity of 38.8% and specificity of 92.2%. The area under the receiver operating characteristic (ROC) curve was 0.78 (95% CI: 0.75–0.80). Five factors were found to be significant correlates of chronic depression: a greater number of co-morbid psychiatric disorders ($\chi^2 = 32.95$, p<.001); older current age ($\chi^2 = 25.00$, p<.001); younger age of onset ($\chi^2 = 16.08$, p<.001); more frequent episodes of depression ($\chi^2 = 5.11$, p<.027); and the first episode of depression occurred after the death of someone close rather than out of the blue ($\chi^2 = 5.66$, p<.021). There was no evidence of multicollinearity between the variables as indicated by the mean Variance Inflation Factor (VIF) of 1.46 and Tolerance values above 0.1. The model was found to be significant (likelihood ratio test $\chi^2 = 279.61$, p<.001) and the odds ratios of all correlates are presented in Table 4.

4. Discussion

In the present study, the lifetime prevalence of chronic depression in community-residing individuals in Australia was 4.6%. A recent United States (U.S.) study which was based on data from the Healthcare for Communities (HCC) survey had a comparable reported lifetime prevalence of persistent depression of 4.0% (Young et al., 2008). The prevalence of chronic depression in both Australia and the United States is considerably higher than the reported Canadian lifetime prevalence of 2.7%, which was derived from the Canadian Community Health Survey: Mental Health and Well-Being

Table 4
Multivariate logistic regression model predicting lifetime chronic depression.

Predictor	OR	CI (95%)	t	p
Current age	1.04	1.02–1.05	5.00[a]	<.001
Female gender	1.00	.63–1.57	−.02	.985
Greater number of episodes (>3)	1.75	1.07–2.86	2.26[a]	<.027
Unemployment	1.60	.97–2.64	1.87	.067
Suicidal ideation	1.05	.52–2.14	.15	.883
Suicide attempt(s)	.61	.33–1.12	−1.62	.110
Psychiatric co-morbidity	1.42	1.26–1.61	5.74[a]	<.001
Medical co-morbidity	1.04	.94–1.15	.81	.420
Traumatic load	1.02	.92–1.12	.33	.741
Current disability (WHODAS12)	1.01	.99–1.03	.97	.338
Current psychological Distress (K-10)	1.02	.97–1.06	.74	.464
Severe symptoms	1.14	.60–2.18	.42	.678
Age of onset	.97	.95–.98	−4.01[a]	<.001
Precipitating factor of first episode				
Out of the blue (reference category)				
Death of someone close	2.60	1.16–5.79	2.38[a]	<.021
Stress	1.48	.79–2.78	1.24	.221
No. of family members with depression	.99	.75–1.32	−.05	.959

Abbreviations: OR = odds ratio; CI = confidence interval.
Coding: chronic (1.00) non-chronic (0.00).
[a] Significant finding.

(2002) (Satyanarayana et al., 2009). The lower lifetime prevalence of chronic depression in the Canadian survey is likely to be the consequence of it not including individuals with Dysthymic Disorder. The inclusion of individuals with Dysthymic Disorder makes the present study more clinically relevant to the revisions proposed for DSM-5.

The current study found that higher rates of psychiatric co-morbidity, older age, a younger age of onset, more frequent episodes of depression and a first episode of depression that developed after the death of someone close were significant correlates of chronic depression. In line with previous findings, greater psychiatric co-morbidity had the strongest association with chronic depression (Satyanarayana et al., 2009). The link between chronicity and complex psychiatric co-morbidity is well established (Bagby et al., 2008; de Graaf et al., 2004) and could be viewed as a vulnerability that precedes chronic depression, a complication due to chronicity, or as a modifier that influences the presentation of the depressive episode (Bagby et al., 2008).

Anxiety disorders were the most common co-morbid conditions, with chronically depressed individuals having higher rates of generalized anxiety disorder, obsessive compulsive disorder and post-traumatic stress disorder compared to non-chronically depressed individuals. These findings are consistent with previous work that found anxiety disorders to be the most common co-morbid disorders with MDD (de Graaf et al., 2004; Rush et al., 2005). Individuals may have a biological predisposition to both a chronic course of depression and more anxiety features.

The "kindling" hypothesis has been used to investigate the relationship between recurrent episodes of depression and chronicity. This hypothesis suggests that life stress is strongly associated with the first episode of depression rather than recurrent episodes of depression (Monroe and Harkness, 2005). It is thought that recurrent episodes may emerge autonomously to stress where stress is no longer required to precipitate an episode (Monroe and Harkness, 2005). Alternatively, recurrence may be due stress sensitization where even minor stress may trigger the onset of a depressive episode (Monroe and Harkness, 2005). The current study found that chronic depression was associated with a greater number of episodes and a first episode of depression precipitated by the death of some close. Chronic depression was also associated with a greater lifetime traumatic load and a higher prevalence of PTSD in the bivariate analyses. These findings may provide support for the kindling hypothesis and may suggest that the effect is more evident in individuals with chronic depression than non-chronic depression.

A younger age of onset was also a significant correlate of chronic depression. Some investigators have suggested that an earlier age of onset is indicative of a more chronic course of depression and is a heterogeneous feature among all chronic depressive subtypes (Klein, 2010).

In keeping with the findings of others (Gilmer et al., 2005; Rush et al., 1995), we found that older current age was associated with increased risk of lifetime chronic depression. This might be a temporal exposure artifact, as older people have had a longer time to manifest chronic depression, a condition with a variable age of onset. Alternatively, chronic depression might be linked to older age or to some unmeasured factor linked to older age. We favor the former explanation because most epidemiological studies demonstrate falling rates of depression among community-residing older people (Charles et al., 2001; Kessler et al., 2010). However, cerebrovascular disease, including stroke and white matter ischemic changes, is associated with older age, a chronic course and treatment resistance of depression (Rao, 2000; Sheline et al., 2010).

The overall lifetime prevalence of self-reported mental health service use for individuals with affective disorders in Australia is 58.6% (Burgess et al., 2009). In the current study, most of the non-chronically and chronically depressed individuals had seen a general practitioner (primary care practitioner) about their mental health problems during their lifetime, but less than half of the chronically depressed individuals reported consultations with a psychiatrist during their lifetime. In relation to this finding, it is worth noting that Australia has a universal health insurance system that covers both primary and secondary care. A recent U.S. multi-site study of the adequacy of prior antidepressant treatment found that despite high symptom severity and a chronic course of depression, only one third of chronically depressed individuals had ever received an adequate antidepressant trial (Kocsis et al., 2008). The current study found that 42.2% of chronically depressed individuals felt they had no need to utilize the mental health services that were available to them. The nature and accessibility of mental health services may need to be modified to target chronic depression more effectively.

Some caveats are warranted. The model we developed in the current study had low sensitivity but a high specificity, indicating that other, unmeasured, factors are likely to be important in distinguishing between chronic and non-chronic depression. These may include biological factors, personality traits and current psychosocial stressors. The nature of our secondary analysis, which was based on cross-sectional self-report data elicited by trained lay interviewers using structured interviews, did not allow for a detailed depiction of the course of chronic depression. Also, the cross-sectional data collection did not allow for a detailed analysis of the temporal relationship between the chronicity of depression and many clinical variables. There were also some inherent limitations in the definition of chronic depression that we employed and in the variable we used to split those individuals with lifetime MDD into chronic and non-chronic types of depression. However, the variable was chosen in line with the WMH-CIDI 3.0 recommendation for identifying persistence and also because the variable had been used to identify chronicity in an earlier Canadian study (Satyanarayana et al., 2009). The inclusion of individuals with a lifetime history of Bipolar Affective Disorders is consistent with the proposed DSM-5 diagnosis of Chronic Depressive Disorder but may limit the comparability of the current paper with earlier Chronic Depression literature. However, the inclusion of individuals with a lifetime history of Bipolar Affective Disorder improves the generalizability of the paper to the general population in which co-morbid diagnoses are highly prevalent. The survey relied heavily on personal recall and it is unclear the extent to which current

symptoms or underlying negative temperament might have affected recall.

Despite these limitations, the significant differences identified between chronic and non-chronic depression, and the evidence of higher current disease burden with lifetime chronicity, lend support to the proposal for a DSM-5 category of Chronic Depressive Disorder. As others have suggested (Klein et al., 2006; McCullough et al., 2003), there may be some utility in collapsing the various chronic depressive subtypes into one entity, which focuses on the chronicity of the depressive presentation rather than on episodic and remitting features. The levels of psychological distress, functional disability and disease burden posed by chronic depression are considerable. The existence of a distinct nosological category of Chronic Depressive Disorder might facilitate greater public health emphasis on this high-prevalence condition.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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